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EFFECTS OF GIVING NITROGEN MUSTARD BY DIFFERENT ROUTES TO RATS RECEIVING WALKER 256 CELLS INTRAPORTALLY, INTRAPERITONEALLY, AND SUBCUTANEOUSLY

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THE initial report[2] from this laboratory indicating that nitrogen mustard was effective in decreasing the "takes" of Walker 256 cells dealt only with animals having cells injected into a branch of the portal vein.

Since cancer cells may be disseminated into areas other than the portal system, such as into operative wounds, the peritoneal cavity, etc., therefore it also would seem important to study the antitumor effect of nitrogen mustard against tumor cells injected into the subcutaneous and intraperitoneal cavities. Nitrogen mustard will induce regression in only a small portion of patients with established tumors. Experimental[2] and clinical[5, 6] evidence from this laboratory suggests, however, that this drug may kill disseminated tumor cells circulating in the portal and systemic vessels.

In designing the present study to determine the prophylactic effect of nitrogen mustard on cells inoculated subcutaneously and into the peritoneal cavities, it seemed highly desirable to compare these results with those obtained against cells injected into the portal system. Likewise it appeared important to compare the therapeutic efficiency of the intraportal, intraperitoneal, and systemic routes.

It is hoped that the knowledge derived from this experimental study could be applied to the clinic problem of adjuvant chemotherapy at the time

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of operation and provide a basis for the selection of the optimum route of drug administration.

MATERIALS AND METHODS

Female Sprague-Dawley rats weighing 130 to 170 grams were used. A fresh tumor cell suspension of Walker's 256 carcinosarcoma was prepared by the method described by Lucké and his associates.[3] Ten thousand cells suspended in 0.5 ml. of saline were given to each rat. Aseptic technique was used for the preparation of the cells and during the operation. The rats were anesthetized with 0.3 per cent Nembutal injected intraperitoneally. The abdomens of all the rats were opened to subject each of the animals to the same operative stress. In one set of rats the intraportal injection of cells was made directly into the portal vein, while the intraportal nitrogen mustard was injected into a superior mesenteric vein, in order to expose all of the proximally injected cells to the action of this drug. Freshly prepared nitrogen mustard, 0.5 mg. per kilogram, was the standard dose used throughout the study. Rats receiving intraperitoneal tumor cells and nitrogen mustard received these agents directly on the surface of the intestines through the open abdominal incision. Rats receiving the subcutaneous inoculation of cells had the suspension introduced into a previously prepared subcutaneous pocket in the left flank. Following the inoculations of cells and/or nitrogen mustard, the wounds were closed with running cotton sutures.

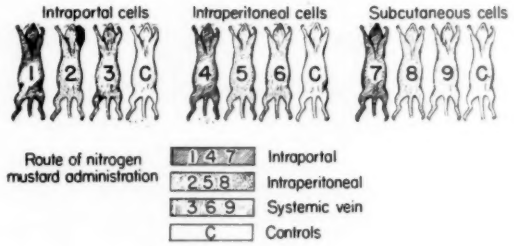

Fig. 1.—Plan of experiment showing the group of rats studied.

Twelve groups of rats were studied as shown in Fig. 1. Each group was comprised of approximately 30 to 40 animals. Twenty-four rats were operated upon at one time. The animals were placed in sets of four with the fourth animal of each set acting as a control. In the first set, cells were injected intraportally; in the second, intraperitoneally; and in the third, into a subcutaneous pocket. Nitrogen mustard was injected into the first rat of each set intraportally, into the second set intraperitoneally, and into the third through the femoral vein. Nitrogen mustard was administered one hour after the cells.

Rats dying within 48 hours of operation were excluded from our results. Animals dying before or killed at 30 days were autopsied to determine the presence of tumor. Representative histologic sections were made.

RESULTS

The results are shown in Tables I and II.

Nitrogen mustard injected intraportally, intraperitoneally, and into the femoral vein (Groups 7, 8, and 9, Table II) had *no effect* against cells injected into the subcutaneous pockets (100 per cent "takes").

TABLE I. INCIDENCE OF "TAKES" OF THE WALKER 256 TUMOR WHEN NITROGEN MUSTARD WAS GIVEN ONE HOUR AFTER THE CELLS

	INTRAPORTAL CELLS				INTRAPERITONEAL CELLS			
	GROUP 1	GROUP 2	GROUP 3	GROUP C	GROUP 4	GROUP 5	GROUP 6	GROUP C
Route of HN_2 administration	Intraportal	Intraperitoneal	Systemic venous	Control	Intraportal	Intraperitoneal	Systemic venous	Control
No. of rats with "takes"	24	18	25	42	25	13	27	33
No. of rats without "takes"	19	25	20	2	2	17	3	0
Total animals	43	43	45	44	27	30	30	33
Per cent "takes"	53.5	41.2	55.5	95.5	92.6	43.3	90.0	100
Probability*	<0.001	<0.001	<0.001	—	NS	<0.001	NS	—

*Probability of this group and control groups were from the same population.

TABLE II. INCIDENCE OF "TAKES" OF THE WALKER 256 TUMOR WHEN NITROGEN MUSTARD WAS GIVEN ONE HOUR AFTER THE INOCULATION OF CELLS IN SUBCUTANEOUS POCKETS

	GROUP 7	GROUP 8	GROUP 9	GROUP C
Route of HN_2 administration	Intraportal	Intraperitoneal	Systemic venous	Control
Number of rats with "takes"	28	28	31	31
Number of rats without "takes"	0	0	0	0
Total animals	28	28	31	31
Per cent "takes"	100	100	100	100
Probability*	NS	NS	NS	NS

*Probability of this group and control groups were from the same population.

Nitrogen mustard was most effective against intraportal and intraperitoneal tumor cells when the drug was injected into the peritoneal cavity. The intraperitoneal injection of nitrogen mustard (Groups 2 and 5, Table I) was followed by 41.2 per cent "takes" in the animals receiving cells intraportally, and 43.3 per cent in those receiving cells intraperitoneally.

Nitrogen mustard was as effective given through a systemic vein as by intraportal injection against intraportal and intraperitoneal tumor cells. When cells were injected intraportally, "takes" occurred in 53.5 per cent of the animals receiving nitrogen mustard intraportally and in 55.5 per cent of those receiving nitrogen mustard via the femoral vein (Groups 1 and 3, Table I).

Cells injected intraportally were more readily killed by nitrogen mustard than those injected intraperitoneally or implanted into subcutaneous pockets. The intraportal injection of cells (Groups 1, 2, and 3, Fig. 1) was followed by

fewer "takes" (53.5 per cent, 41.2 per cent, and 55.5 per cent, respectively, Table I) as compared to the intraperitoneal implantation of cells (Group 4, 92.6 per cent; Group 5, 43.3 per cent, and Group 6, 90 per cent, Table I). No treated animals survived when the cells were placed in subcutaneous pockets (Groups 7, 8, and 9, Table II).

DISCUSSION

Nitrogen mustard was given one hour after the cells because there is at least this time interval during clinical surgery between the removal of the primary malignancy with presumed dissemination of malignant cells and the administration of nitrogen mustard. Nitrogen mustard is inactivated within minutes of its introduction into the body.[5] For this reason, the interval between the injection of tumor cells and of nitrogen mustard is important. Table III shows that the efficiency of nitrogen mustard in preventing "takes" of the Walker 256 rat tumor decreases rapidly when the interval between the implantation of the cells and the injection of nitrogen mustard is increased.

TABLE III. THE EFFECT OF GIVING NITROGEN MUSTARD* AT VARIOUS TIMES ON "TAKES" OF THE WALKER 256 TUMOR† IN THE RAT

INTERVAL BETWEEN GIVING NITROGEN MUSTARD (HN_2) AND CELLS	NUMBER OF RATS T-TREATED C-TREATED	PER CENT TAKES	DIFFERENCE	AUTHORS
6 hours before cells	T 25	T 80	7	Morales and others[6] (1957)
	C 22	C 87		
1 hour before cells	T 47	T 79	15	Morales and others (1957)
	C 49	C 94		
1 minute after cells	T 45	T 18	74	McDonald and others[5] (1957)
	C 48	C 92		
1 minute after cells	T 36	T 19	78	Cruz and others[2] (1957)
	C 38	C 97		
1 minute after cells	T 36	T 0	98	McCredie[4] (1958)
	C 42	C 98		
6 hours after cells	T 27	T 89	11	Morales and others (1957)
	C 27	C 100		
24 hours after cells	T 40	T 73	8	Morales and others (1957)
	C 42	C 81		
48 hours after cells	T 39	T 85	5	Morales and others (1957)
	C 42	C 90		

*Five-tenths milligram nitrogen mustard per kilogram of body weight was injected into the superior mesenteric vein in one dose.

†One hundred ten thousand cells of the Walker 256 tumor were injected into the superior mesenteric vein.

Nitrogen mustard was given intraportally, intraperitoneally, and by a systemic vein, since these routes are being used clinically. Nitrogen mustard was not placed directly into the subcutaneous pockets in this particular study because the local effect of nitrogen mustard and other antitumor substances has already been studied in this department.[1] Malignant cells were injected intraportally and disseminated into the intraperitoneal and subcutaneous pockets since these areas of cancer cell contamination may occur during operation.

The fact that nitrogen mustard was of no value against cells injected into subcutaneous pockets (100 per cent "takes"), in this experimental study, emphasizes the great danger which may result from inadvertent subcutaneous tumor cell contamination of wounds during dissections particularly involving radical neck and breast surgery. Repeated observations have shown that a higher "take" incidence may be expected in treated animals when tumor cells are disseminated into traumatized host tissue (here, in surgically prepared pockets) as contrasted with the incidence of "takes" occurring in similarly treated animals when dissemination of the cells is caused directly by percutaneous needle inoculation. The dosage of nitrogen mustard used, namely, 0.5 mg. per kilogram for one dose, is actually a small one; preliminary experiments indicate that a larger amount (in divided doses) will be slightly more effective; additional work with larger doses is being carried out.

The greater effectiveness of nitrogen mustard against cells injected into the liver and peritoneal cavity than when inoculated into subcutaneous pockets is presumably explained on the basis of increased local immunity in the former two sites; it must be admitted, however, that contact of cells with the drug is more direct in the liver and peritoneal cavity.

SUMMARY

The effects of nitrogen mustard were studied when it was administered intraportally, intraperitoneally, and by a systemic vein, determining "takes" of the Walker 256 tumor in the rat. The effect of nitrogen mustard was also observed on cells implanted intraportally, intraperitoneally, and into subcutaneous pockets. It was found that:

1. Nitrogen mustard administered by the intraperitoneal, intraportal, or systemic routes was equally effective against tumor cells disseminated within the portal system.

2. Intraperitoneal nitrogen mustard administration was significantly superior to nitrogen mustard given by the intraportal or systemic routes in preventing "takes" from tumor cells disseminated into the peritoneal cavity.

3. Nitrogen mustard had no effect against tumor "takes" from cells implanted into a subcutaneous pocket, whether the drug was injected intraportally, intraperitoneally, or into the femoral vein.

CONCLUSION

Observations from this study indicate that intraperitoneal nitrogen mustard administration is the route of choice in preventing "takes" resulting from the dissemination of tumor cells within the portal vein or peritoneal cavity.

Systemic administration of nitrogen mustard was totally ineffective in preventing "takes" from tumor cells planted within subcutaneous pockets. However, additional work is being done on the use of a larger amount of drug in divided doses.

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REACTION OF THE GREAT OMENTUM OF THE RAT TO PIPE TOBACCO TAR, INCLUDING THE FORMATION OF GIANT CELLS

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INTRODUCTION

THE lungs, because of the presence of lymphatic tissue, potential histiocytes or macrophages (septal cells), and capillaries, which can strain megakaryocytes, granular leukocytes, and foreign substances from the blood circulating through them, constitute a very reactive type of organ and tissue.

In view of the controversy regarding the reaction of lungs to cigarette tar when the smoke is inhaled, we thought it might be of interest to study the effects of tobacco tar when applied directly to another type of very reactive and embryonic tissue, namely, that of the great omentum of the rat.

The rat's omentum contains many lymphocytes, especially in the "milky spots," of various types and sizes, which are scattered through the membrane, and are especially large along the blood vessels in the thicker parts of the organ. These lymphocytes are associated with histiocytes, monocytes, undifferentiated mesenchyme[12] along the capillaries, a few granular leukocytes, and, especially in the rat, numerous tissue mast cells. Because of the histiocytes and lymphocytes which are potential macrophages,[2, 12] these "spots" are centers which show marked reaction to colloidal dyes and other foreign and endogenous substances present in the peritoneal fluid. According to Hamazaki,[6] the histiocytes of the spots form an upper layer in direct contact with the fluid (due to lack of mesothelium over this layer in some of the spots). This arrangement facilitates the removal of foreign material from the fluid, making the milky spots the most important portion of the omentum for this function, according to Webb.[20]

Maximow[12] states that the fibrocytes of the omentum are more undifferentiated and less specialized than those of the loose subcutaneous connective tissue and that they differ in appearance. Research in this laboratory[16] has shown that the fibrocytes of the omentum when stimulated may round up and form free histiocytes. This was also claimed by Schott.[19] They do this spontaneously when they participate with the histiocytes in the formation of new milky spots in young animals. This may also occur in the loose subcutaneous tissue,[4, 14] but requires a more severe stimulus than in the omentum.

A substantial quantity of a foreign substance, such as the tar which we used, when placed on the surface of the omentum, will cover regions of variable structure. The subjacent regions are: (1) the thinnest, avascular portion of

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the omentum, containing very few free cells, (2) one or more of the smaller milky spots, and (3) a portion of the thick fatty part with abundant perivascular lymphatic tissue.

In the account which follows, we shall present the observations we have made to date. The study is being modified and extended.

MATERIAL AND METHODS

Four adult female rats, 2 pregnant and 2 nonpregnant, were used for spread preparations of the normal omentum. These were made by placing filter-paper rings on the surface of the free portion of the omentum. The part of the membrane adhering to the ring was then cut out, and ring and tissue were placed in Helly's Zenker-formol for one-half to one hour. Staining, dehydrating, and clearing were done while the tissue remained stretched on the ring. The ring was cut away in xylol and the tissue was mounted as though it were a section.

Tar was placed on the omentum of 3 adult female rats, aged 3½ months, 8 months, and one year, respectively. Tar scooped from the stem part of a pipe bowl was dried to the consistency of putty, worked to a pellet, and placed on the ventral surface of the omentum. The free edge of the omentum was folded upward to cover the tar and held in place with 2 Michel wound clips, each placed about 1 cm. lateral to the tar. The ventral surface of the omentum was, therefore, in direct contact with the tar, and the dorsal surface formed the covering of the nodule composed of tar pellet and omentum.

This nodule was excised at autopsy and fixed in Helly's fluid for 6 hours and washed in running water for 24 hours. The subsequent procedure was according to the usual technique for this type of fixation. The entire nodule was embedded in paraffin and cut into serial sections. Eight to 10 sections from different parts of the ribbon were selected for mounting and staining in hematoxylin and eosin or with Dominici's eosin-orange G-toluidin blue stain.

OBSERVATIONS

Our observations on the 4 stretch preparations of the normal omentum need not be presented in detail, but they confirmed the observations recorded by other workers. Only a few of them can be mentioned here. Maximow[12] gave a well-illustrated general description of the histology of the omentum of man and mammals. Hamazaki[6] studied the different types of milky spots in the rat and other mammals and noted the reactions of the spots to the subcutaneous injection of lithium carmine. Webb[20] studied the reactions of the spots to intraperitoneal injections of egg albumen and blood charcoal. Poynter[17] described the development and anatomy of human omentum. He also noted that dye injected into the peritoneal cavity of animals is absorbed by the small vessels of the omentum.

The development of the milky spots in young rabbits was described briefly by Dr. Emily Payne, who concluded that the fibrocytes give origin to dye-storing mononuclears which transform into the histiocytes, lymphocytes, and plasma cells of the older milky spots.

Myelocytes, erythroblasts, and megakaryocytes have been described in the omentum of young animals by a number of authors, among them Pardi,[15] Melissenos,[13] Jolly,[10] and Maximow.[12]

We used the stretch preparations only for general orientation. We noted the great variation in size, type, and number of the milky spots in different rats, as have others, and the difference between the isolated spots of the thinner portion of the membrane and the thick perivascular mass of cells in the thicker, fatty portion. We also found erythroblasts and myelocytes in the younger animals. Our main interest was in the reactions of the omentum to the tar.

At autopsy the omentum of each of the 3 rats with a tar pellet contained 3 nodules in line. The central one was the pellet covered by the thickened omental tissue. The 2 lateral ones were the wound clips covered by a thick overgrowth of new tissues and granular leukocytes. The abdominal organs were of normal appearance, and a blood smear made at this time was normal.

Rat 5, Aged One Year, Tar in the Omentum for 8 Days.—Serial sections were made through the entire nodule consisting of the tar pellet and surrounding thickened omental tissue composed chiefly of dense or loose fibrous tissue infiltrated with lymphocytes, histiocytes, and heterophil leukocytes. Sections from different parts of the ribbon show some variation in the amount of fat and number of free cells in this tissue which forms a capsule around the central mass of tar. A typical section shows the following features:

The tar pellet is broken up to some extent by ingrowth of tissue which has become necrotic and eosinophilic, or transformed to a clear jellylike mass. Ingrowth of fibroblasts which are large and basophilic and have long, pointed processes can be seen in some places. Some of these cells are in mitosis.

The tissue around the central masses of tar varies in different places of the same section, probably due to variations in structure of the normal omentum. A dense layer of heterophils surrounds the main mass of tar. The outer cells of this layer have degenerated while those of the inner portion may be well preserved. There is considerable variation in the character of the tissue surrounding the outer layer of leukocytes. There may be a wide band of eosin-stained necrotic tissue composed of degenerating histiocytes, fibrocytes, and heterophils, which remain as granular bits of eosin-stained substance after they have lost their nuclei. The layer of leukocytes is surrounded by a dense layer of connective tissue, which has fibers and fibrocytes showing parallel circular arrangement with reference to the central mass of tar and which is infiltrated with heterophils, lymphocytes, and histiocytes (Fig. 1). This dense capsule of fibrous tissue contains some small masses of tar. Some of this tar is contained in histiocytes, but much of it is free. A large mass of tar is shown in Fig. 1. This mass has histiocytes at its periphery and a multinucleated giant cell in its center. Much of this tar seems to be free. There is little or no tissue reaction around the tar contained in the dense capsule.

In some parts of the section, instead of a dense capsule, the tissue is of loose or edematous texture and shows new growth of fibrocytes, which in some places penetrate the necrotic tissue. In other places there is a layer of fat surrounding the necrotic tissue.

The character of the tissue varies a great deal as one moves from the dense capsule or fat surrounding the necrotic area to the outer surface (dorsal). In places the dense fibrous tissue extends to the surface; in other regions the tissue is very edematous; and in still others there is much fat. Heterophils and lymphocytes infiltrate most of these tissues, while histiocytes tend to be bunched.

While there are small masses of tar in various regions at some distance from the main central mass, there is no direct evidence that there has been diffusion of tar through the tissue that might have become liquefied. However, a distant effect is proved by edema, migration of granulocytes, and small areas of necrosis. Some of the scattered accumulations of tar have been carried by macrophages, but in other places the tar seems to be free. As some histiocytes contain tar, it may be assumed that the free tar was transported by histiocytes which liberated it when they disintegrated.

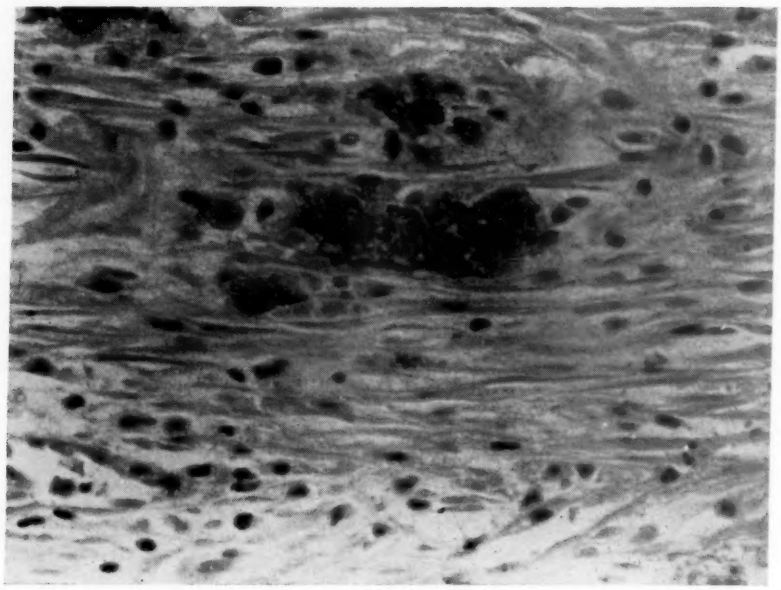

Fig. 1.—Isolated mass of tar in the peripheral dense omental connective tissue surrounding the central tar pellet. The ring of nuclei in the center of the tar indicates beginning giant-cell formation. Rat 5, tar in omentum 8 days.

It is evident that exposure of the omentum for 8 days induces a more extensive and varied reaction than could be expected from an inert foreign body. The character of the reaction changes markedly when tar is left in the omentum for a longer period, as will be seen in Rat 6 in which a tar pellet remained in the omentum for 15 weeks.

In the rat exposed to tar for 8 days, the free portion of the omentum which was folded over the tar pellet forms, with the underlying portion, a complete capsule about the central mass of tar and leukocytes. There is no break or other indication of the line of fusion between the free folded edge of the omentum and the flat portion on the other side of the pellet.

Rat 6, Aged 3½ Months, Tar in Omentum for 15 Weeks.—In this rat the reaction to the tar has progressed much farther than in Rat 5 and shows some

remarkable differences in type. Sections through the central portion of the tar pellet and surrounding omentum show a round and rather dense cellular and fibrous body within a denser connective tissue capsule. This is completely surrounded by a very loosely organized tissue containing a few small arteries and veins, some of which have very thick walls, much thicker than any seen in Rat 5. Fat is not present in this loose tissue or in the central dense portion of the section. The most interesting feature of this outer loose tissue is the presence of the peculiar structures shown with low power in Fig. 2. The central body contains very few of these structures which are located in its dense capsule or in contact with its inner surface. As in Rat 5, there is no indication of a line of fusion of the folded part of the omentum with the rest of the membrane.

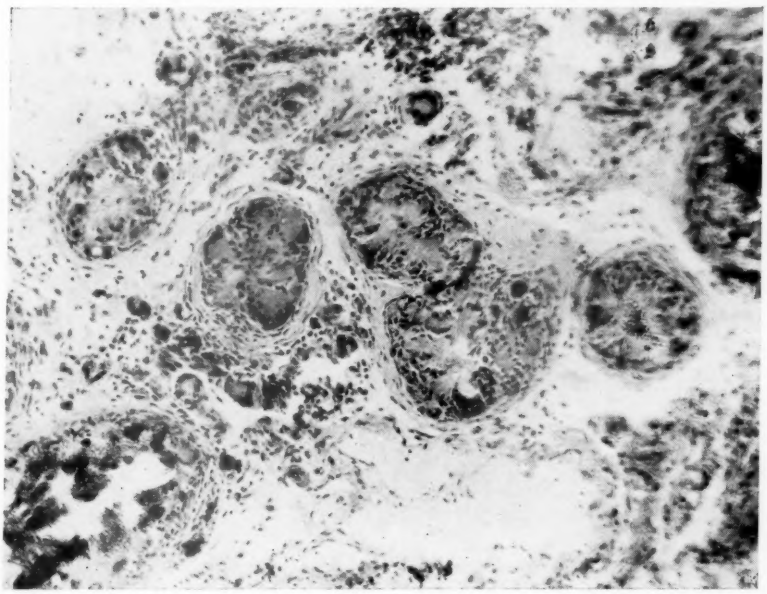

Fig. 2.—The encapsulated structures which are numerous in the loose omental tissue surround the denser inner body containing the remains of the tar pellet. The capsules contain giant cells and interstitial cells (between giant cells) which extend their cytoplasmic processes into the center of the capsule. Many of the capsules contain tar (black in the photograph). Rat 6, tar in omentum 15 weeks.

The tissue within the capsule shows considerable variation in different regions. In some places there are wide-branching bands of connective tissue with marked affinity for eosin. Free cells are not numerous in this region. In other portions the connective tissue network is composed of much finer strands, and there are more free cells. In other regions there is little or no fibrous connective tissue, and the tissue seems to be held together by the processes of branching fibrocytes. Free cells of various types are numerous in this region. In other segments of the inner body the tissue is rather dense with slender connective tissue fibers and cells which tend to assume a parallel arrangement. Free cells are numerous.

The free cells distributed throughout the central body are of various types. Small round cells having nuclei with thick membranes and abundant chromatin seem to be small lymphocytes. Some of these cells with more abundant cytoplasm are probably developing to histiocytes (polyblasts of Maximow). Larger

cells with large leptochromatic nuclei are histiocytes or macrophages, since many of them contain fine tar granules dispersed through their cytoplasm. These cells tend to be grouped in certain areas, although some are scattered through much of the tissue. Heterophils occur in larger and smaller groups, some of which contain tar in their centers. Where there is no tar it is assumed that the section has passed to one side of the tar.

A few solitary giant cells and their developmental stages occur in the denser portion of the tissue. They are formed by the fusion of histiocytes or fibrocytes. The histiocytes which form giant cells do not contain tar granules, and tar was not seen to be associated with these solitary giant cells but does occur in some of the encapsulated giant-cell structures that are illustrated in Fig. 2. In the central body these occur only within or just under the capsule.

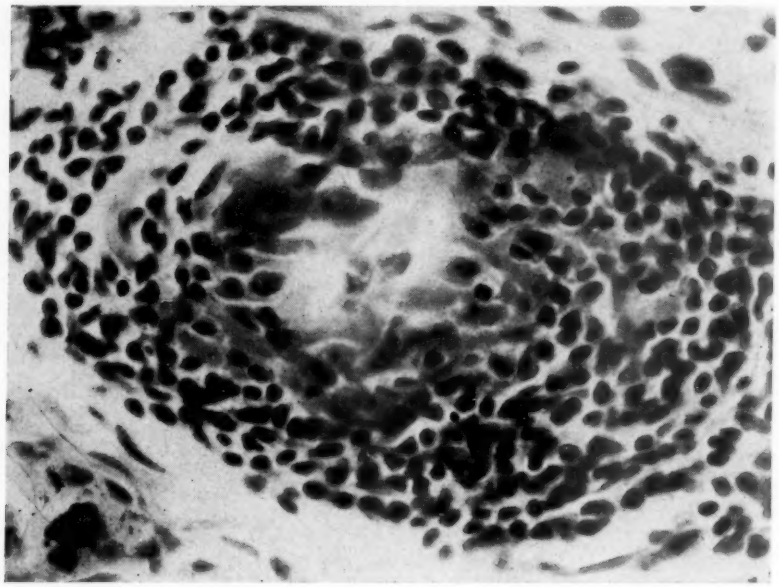

Fig. 3.—Giant-cell development in the center of a dense group of lymphocytes. The central lymphocytes increase their cytoplasm and often the size of their nuclei, and fuse to form giant cells (upper left of center). Rat 6.

There is no large central mass of tar as in Rat 5. Instead the tar has been scattered in larger and smaller masses in the central body and in the outer loose tissue. In the central body most of these masses of tar are surrounded by dense accumulations of heterophils. Small masses of tar are often without the associated heterophils. Only a few heterophils are scattered through the tissue as individual cells.

The encapsulated structures shown with low power in Fig. 2 are concerned with the formation of giant cells. In some, as in the lower left of Fig. 2, their formation seems to be a direct reaction to the presence of tar which may be free or within cells. In this figure it is dispersed in the cytoplasm in the form of small black granules. In Fig. 8 the central mass of tar seems to be partly free and partly intracellular, and in Fig. 5 (lower left) most of it seems to be free.

Fig. 3 shows how some of the encapsulated structures are developed from a dense aggregation of small round cells which appear to be small lymphocytes.

These cells enlarge, their nuclei also enlarge and tend to become leptochromatic with a central nucleolus, and the cytoplasm develops branches and processes, some of which may be very long and which may fuse to form the cytoplasm of a giant cell. This transition begins in the center of the group of cells and gradually works outward, as shown in the figure. The central clear area contains some of the cytoplasm projecting from the inner cells. Fusion of some of these transformed cells with their large pale nuclei to form an early giant cell is seen at the left of the pale center.

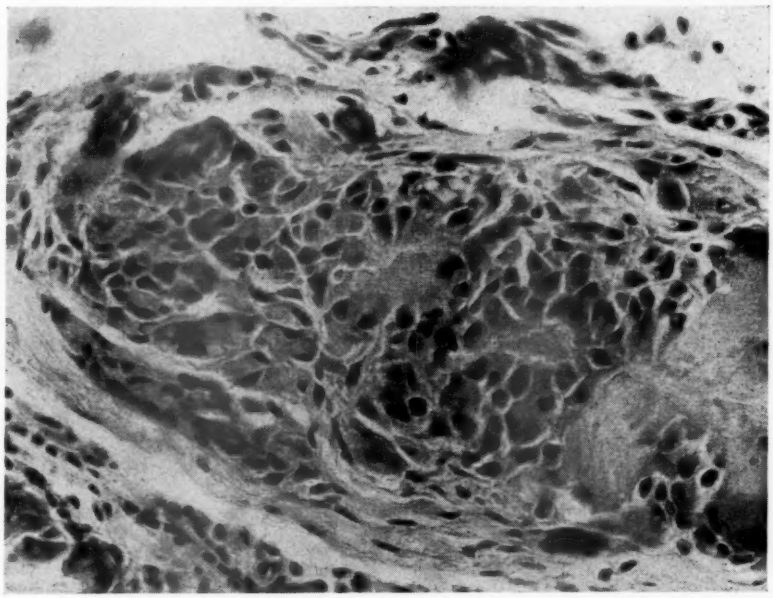

Fig. 4.—Early stage in the formation of an elongated capsular structure. Slightly to right of center, cells resembling polyblasts have assumed circular arrangement and have extended their processes into the center of the circle. An earlier stage of a similar arrangement is in center of figure. Beginning capsule formation. Rat 6.

Fig. 4, with a lower magnification, shows a group of lymphoid cells in the various transformation stages in which they develop a large amount of cytoplasm, often in the form of broad processes extending in one direction from the nucleus. Such cells often form a circle with their broad processes directed toward the center. An arrangement of this type is shown slightly to the right of the center of the figure. The material in the center is composed of the processes of these cells. Another incomplete area of this type is in the center of the figure. In this case most of the cells were not on the level of the section. Fusion of the cells in the circle will result in the formation of a giant cell similar to the large ones of Figs. 9 and 10. The early stage in the development of the connective tissue capsule which surrounds most of the later reaction centers is evident in this figure.

Fig. 5, with higher magnification, shows the transformation stages of the cells in greater detail, and different stages in their fusion to form giant cells. One large giant cell with many nuclei and containing some tar granules is seen slightly below and to the left of the center of the figure.

The local fibrocytes are involved in this type of reaction, along with the transformed smaller lymphoid cells, some of which are seen in the photograph. A dense group of lymphoid cells, similar to the one in Fig. 3, could hardly serve as a precursor to a reaction center of this type.

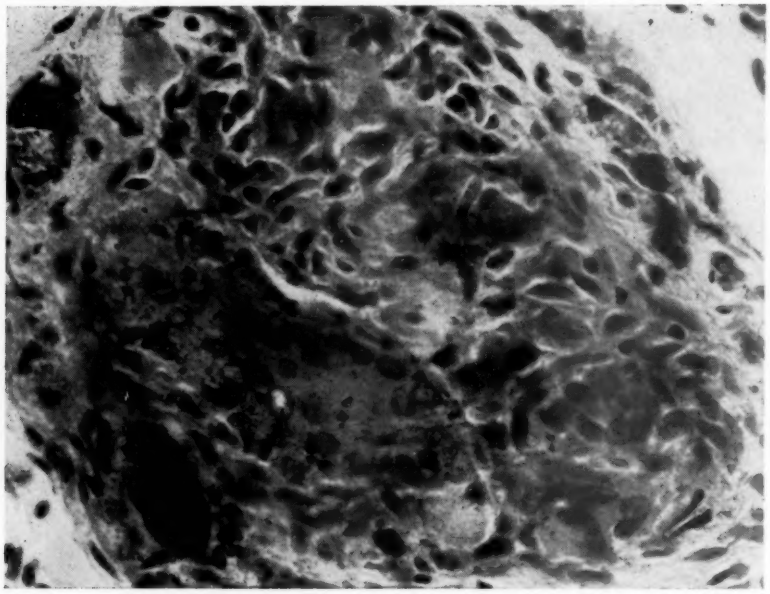

Fig. 5.—A reaction center in which fibrocytes and histiocytes participate in the development of giant cells. A foreign-body type of giant cell contains tar granules at lower left. Rat 6.

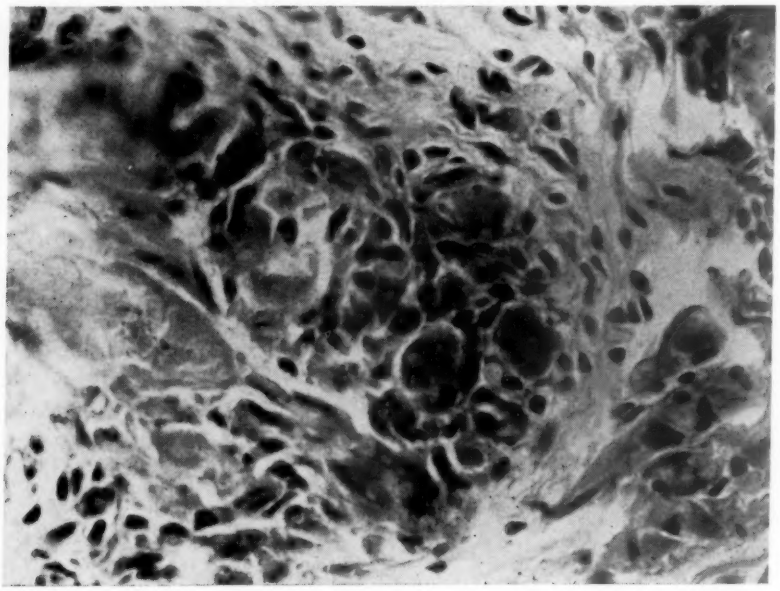

Fig. 6.—Reaction center developing in close association with a mass of tar (the gray material at left). Rat 6.

Fig. 6 is a photograph of a reaction center in proximity to a pale mass of tar in the left-hand portion of the figure. Both lymphoid cells and fibrocytes are involved in this center. Two small giant cells and early stages in the formation of others are seen.

Fig. 7 shows a portion of an elongated center with cells which extend their processes into a space containing material derived from the processes of these cells. In some instances the tubelike structures resemble gland ducts containing secretion. Where the cells are close together, they suggest a columnar epithelium lining the "duct." However, their processes can be traced into the lumen to form the "secretion," and some of them are involved in giant-cell formation, as in Fig. 7. These elongated reaction centers are surrounded by firm capsules, indicating that they are older centers. There is some evidence that neighboring rounded centers can fuse to form the elongated structures (Fig. 2, center).

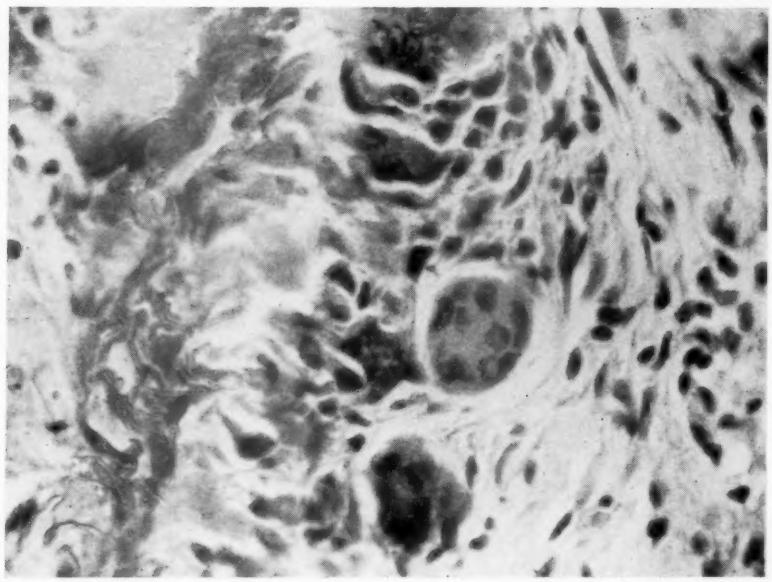

Fig. 7.—A portion of the wall of a tubular encapsulated structure with cell processes extending into the lumen. Giant cells of several types. Incomplete capsule to the right. Rat 6.

The dark mass of tar in the center of the encapsulated structure in Fig. 8 is probably responsible for the localized reaction. Some large, pale nuclei that can be seen at the right edge of the tar and in the center suggest that much of the tar is in macrophages. The gray material surrounding the tar is a product of the cells in the wall of the structure. Giant-cell formation has begun (upper left).

The field illustrated in Fig. 9 is of special interest. Below the large giant cell, extending in a southwesterly direction, are 4 groups of closely approximated nuclei which belong to cells that are to form new giant cells. The groups of smaller nuclei may be, in part, the result of amitosis, although we could not find good evidence for this, and we did not see mitoses in any of these reaction centers. In the lower group the nuclei are in cells which are fusing to form a larger giant cell. The two cells at the lower right of this group have abundant cytoplasm which probably will fuse with the complex at the upper left of this group.

Other cells, like the one at *C*, may join this group to complete the development of a large giant cell. Cells of this type may be closely associated before

they produce long, slender or broad cytoplasmic processes which will fuse to form the cytoplasm of a giant cell of which there may be several enclosed within one capsule (Fig. 2). The early stages of this process are shown in Figs. 4 and 7. Other cells of this type may form their cytoplasmic processes while they are isolated in the connective tissue. Cell *C* is a good example of a cell having an

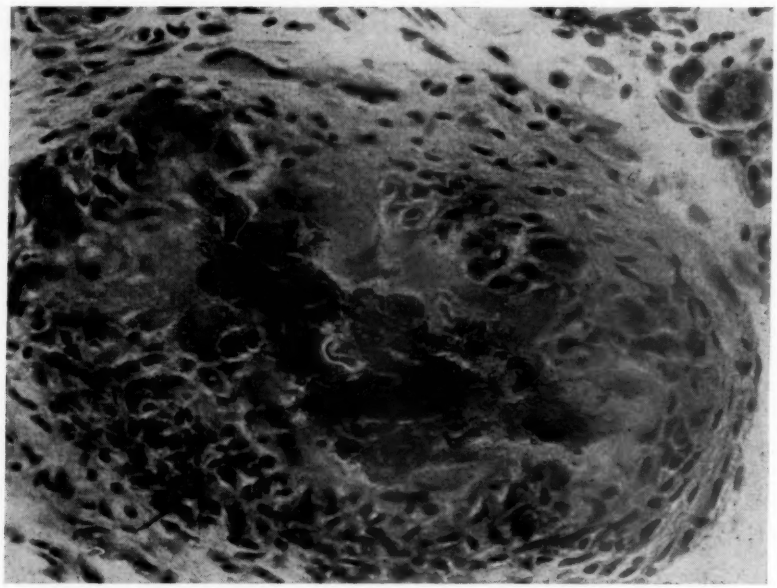

Fig. 8.—A capsule which has developed about a mass of tar. Rat 6.

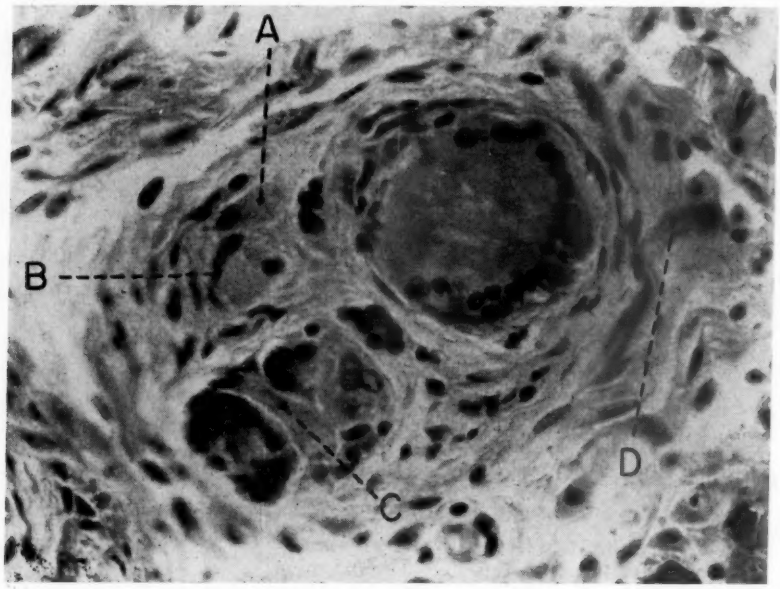

Fig. 9.—A group of giant cells of different types surrounded by a dense capsule. Cells *A*, *B*, *C*, and *D* with long cytoplasmic extensions. Similar cells may fuse to form giant cells with extended cytoplasm, which may fill the center of a capsule. Cell *C* is of special interest because of the extent of its cytoplasmic process. Nuclei always remain at one end of such cells. After fusion of the cells these nuclei remain in the cell bodies of large giant cells. Rat 6.

extremely long process. Other cells of the type are seen at *A*, *B*, and *D*. Cell *A* has a very broad process, cell *B* is long and narrow, and cell *D* is broad. Cell *D* has a large nucleus, so may have been derived from a large histiocyte or fibrocyte rather than from the smaller lymphoid cells which seem to be the progenitors of most cells of this type. The nucleus always remains at one end of the cell. It seems likely that the cells with long processes will migrate, become closely associated, and contribute to the formation of a giant cell.

A capsule seems to be forming around the giant-cell complex in Fig. 9. If growth continued, structures similar to those in Fig. 2 would result.

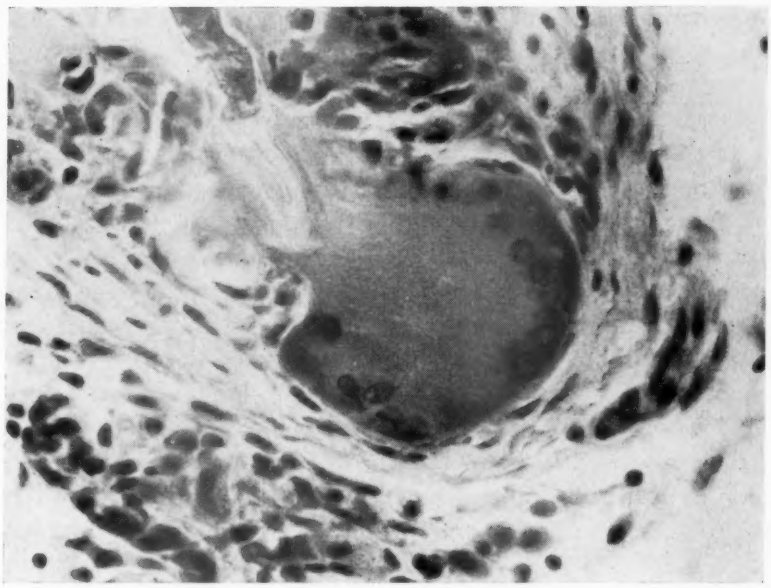

Fig. 10.—A large giant cell of Langhans type extending its cytoplasm for some distance from the body of the cell. Similar cytoplasmic extensions from giant cells and interstitial cells (between giant cells) may fill the center of a capsule. The figure shows one end of an elongated capsule. Rat 6.

The large giant cell in Fig. 10 is of interest because it shows that the cytoplasm of the nucleated sphere may project for some distance through the non-nucleated side of the sphere. This and the processes from separate cells in the walls furnish the central cytoplasmic material of many of the encapsulated structures similar to those of Fig. 2.[2]

DISCUSSION AND CONCLUSIONS

The most interesting results of our experiments are the disposition of the tar, the general tissue reaction, the development of giant cells, and the peculiar structures which result when giant-cell complexes are enclosed by connective-tissue capsules.

The reaction around the tar pellet differs from that which usually occurs when foreign material is introduced in connective tissue. There is a tremendous accumulation of polymorphonuclears about the pellet, which is still present in the rat exposed to tar for 15 weeks, but the usual macrophage reaction does not

follow. A few histiocytes and macrophages do appear outside the ring of granulocytes; most of them are scattered through the tissue or occur in small groups at some distance from the tar. Some of these contain dark brown granules the same color as the tar. While there seems to be some phagocytosis of tar, it occurs to a very minimal degree. However, the tar pellet does get broken up, partly by the ingrowth of connective tissue, as seen in Rat 5. In Rat 6 there are masses of tar in the outlying regions which are not surrounded by heterophils or macrophages. Some of these are in the encapsulated structures (Fig. 2); others are free and seem to induce the development of giant cells.

The tar was not sterilized, which may account for the enormous number of polymorphonuclears which surround the pellet and its central remains. That scattered masses of tar are not associated with heterophils may mean that these bits of tar have become sterile and so do not attract the heterophils but do induce the formation of giant cells. Giant cells are also formed in regions where there is no tar, suggesting diffusion through the tissue of some dissolved material from the tar.

Most of the giant cells are of the Langhans type (Figs. 9 and 10), with nuclei within the outer surface of the cell for about two-thirds of its circumference. These cells seem to be spheres, open at one side where the cytoplasm may project for some distance (Fig. 10). In the encapsulated structures (Fig. 2) this cytoplasm from giant cells may fill the center of the capsule when it is not occupied by tar. A few giant cells are of the foreign-body type, with scattered nuclei, and often contain tar granules (Fig. 5).

In Rat 6 we find variations in the origin and development of the giant cells. Some develop within the central portion of a large accumulation of small lymphocytes, some of which develop an increased amount of cytoplasm and then fuse to form a giant cell (Fig. 3). Other small giant cells develop in the dense connective tissue from a group of 7 or 8 polyblasts (histiocytes), which are also derived from small lymphocytes. Many of the histiocytes form long processes which may or may not be involved in the formation of giant cells (the labeled cells in Fig. 9). They may project their processes into the center of a capsule where they contribute cytoplasm which may fill the center of the capsule (Fig. 7).

Some giant cells not surrounded by capsules are derived directly from fibrocytes (Figs. 5 and 6). The fibrocytes enlarge, develop cytoplasmic processes, separate from adjacent fibrocytes, and then some of them fuse to form giant cells.

Some reaction centers in Rat 6 seem not to be concerned with giant-cell formation. Both lymphocytes and fibrocytes have increased their cytoplasm and assumed more or less stellate shapes. Mitoses do not occur in these centers. In Rat 5 there are centers of very active fibrocytic growth, seen especially where connective tissue is growing into the tar, but also at some distance from the tar. Such growth centers are not encountered in Rat 6. Mitoses are numerous. There is no indication of beginning capsule formation, and there are no giant cells. Capsule formation seems to be associated exclusively with the presence of a group of giant cells. The latter are scarce in Rat 5, and none is encapsulated.

Only a few giant cells of Rat 6 contained tar granules, and these were of the foreign-body type, like the large one at the lower left of Fig. 5. However, many of the encapsulated structures with giant cells contained tar in their centers, but not in the main body of the giant cells. Other encapsulated structures contained no tar, their centers being completely filled with projecting cytoplasm of giant cells and of interstitial cells in the inner wall of the capsule.

Some tar lying free in the tissue has lost much of its color, possibly due to the dissolving action of the alcohol used for dehydration. This may account for complete lack of tar in many regions where giant cells are numerous.

The development of the capsular structures of Fig. 2 is illustrated in Figs. 4 and 5. Cells apparently derived from lymphocytes develop single processes, assume circular arrangement and point their processes toward the center (Fig. 4). Some of these cells fuse to form giant cells, their projecting cytoplasm forming the core of this part of the capsule. Adjacent cells may also fuse to form giant cells, and a fibrous capsule develops around the entire complex. In other cases fibrocytes and histiocytes become stellate shaped and fuse to form giant cells (Fig. 5), which, with neighboring cells, then become surrounded by a capsule. Our sections show many stages in the development of these capsules and their contents. In many instances this development proceeds around tar, but in some there is no trace of tar.

SUMMARY

Pellets of tobacco tar obtained from a pipe were placed on the ventral surface of the omentum of rats. The free edge of the omentum was then folded over the pellet and secured with wound clips. The folded part of the omentum fused with the other portion, and thus formed a complete capsule of omental tissue about the pellet. The pellets, with surrounding omental tissue, were removed at autopsy and sectioned. Pellets remained in the omentum for 8 days in one rat and for 15 weeks in another one.*

Giant cells, mostly of the Langhans type, were very numerous in the rat exposed to tar for 15 weeks. Many of these giant cells, along with lymphocytes, histiocytes, and activated fibrocytes, were surrounded by dense connective-tissue capsules, as seen in Fig. 2. The origin of the giant cells from several sources is described.

The usual macrophage reaction which follows the initial accumulation of granular leukocytes about a foreign substance in connective tissue did not occur in the "tar rats." The tar pellet was broken and scattered through the omental tissue, but there was very little phagocytosis of tar.

The omentum was selected for these experiments because its fibrocytes resemble embryonic mesenchyme in their capacity to react to foreign influences. The project grew out of recent discussion of the effects of inhaled cigarette smoke (tar) upon the lungs.

*In Rat 7 the tar was in place for 19 weeks, and the tissue reaction was less advanced than that observed in Rat 6; the particulars are not presented because the implanted tar was surrounded by an encapsulated mass of pus.

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PSYCHIATRIC OBSERVATIONS ON FIFTY POSTGASTRECTOMY PATIENTS

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THIS is a study of a random sample of 105 postgastrectomy patients called in by the surgeon for surgical postoperative follow-up. Contact was made with 109 patients, the surgeon consulted with 105, and 50 of the 105 were seen by myself for a psychiatric evaluation. The psychiatric evaluation consisted of a 60-minute interview. The patient was informed that the examiner was a psychiatrist and it was explained that he was interested in the emotional aspects of peptic ulcer.

The operation performed on all of the patients was a Billroth I procedure, with a bilateral vagotomy. In the procedure 50 to 60 per cent of the stomach is removed and a new attachment is made to the small bowel. None of the patients interviewed presented recurrence of an ulcer. The group was made up of 42 men and 8 women. They ranged in age from the thirties to the seventies. They came from all levels of the socioeconomic scale.

TABLE I. AGE AT TIME OF OPERATION

	25-35	36-45	46-55	56-65	66-75	TOTAL
Men	8	9	14	8	3	42
Women	2	1	1	3	1	8

TABLE II. MARITAL STATUS AT TIME OF STUDY

	WIDOW(ER)	MARRIED	DIVORCED	SEPARATED	SINGLE
Men	2	35	3	1	1
Women	2	6	0	0	0

All patients had had duodenal ulcers, which had produced severe pain, hemorrhage, or obstruction. All were operated upon by the same surgeon, Dr. Robert Zollinger, Chairman of the Department of Surgery, Ohio State University College of Medicine. The operative procedure was essentially the same mechanically in all cases, as was the physical setup at the time of the operation. At least one year had passed since operation when the patients were seen. Most of them were in the more than 2-year range; some of them were up to 7 years post operation.

The expressed purpose of this psychiatric study was, at the outset, to determine the value of said surgical procedure in removing the symptom—ulcer pain; to determine whether or not other symptoms could be seen to take the place of the ulcer symptom as an emotional economy factor; and to evaluate the

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relationship between the onset or aggravation of the ulcer symptom and the occurrence of important experiences in the environment of the patient. This latter was expanded to include the presence or absence of postgastrectomy complications, sometimes associated with the dumping syndrome (symptoms such as diarrhea, flushing, and inability to gain weight). The dumping syndrome symptoms are the ones the surgeon is most often concerned with postoperatively.[12]

The frame of reference in this study is that of "subjective experience" as differentiated from the chemical, anatomic, and so forth. The patients' verbalizations were utilized to gain evidence of their subjective experiences during their life pre- and postoperatively. No effort was made to give these patients a psychiatric diagnosis. The interviews were carefully structured to avoid suggestive questioning. Rather, the patients were encouraged to talk about themselves so that spontaneous material might be forthcoming which would be a true expression of their thoughts and feelings.

A duodenal ulcer is conceded by many internists and psychiatrists to be a psychosomatic illness, psychosomatic meaning the physical expression of anxiety deflected into a body organ with the resultant development of physical disease. No attempt is made to clarify any specificity factors in this study. Psychosomatic illness is accepted as being a concomitant of anxiety without being the reducer of the intensity of this anxiety. The psychosomatic approach in this study was along the lines suggested by Galdston[6] and others,[1] which expresses that the human organism must be seen as a dynamism which in its over-all interactions with its environment is acted upon even as it acts and is affected even by the modifications it makes in its environment. So seen, the postgastrectomy patient is removed from the single cause-and-effect system of purely organic medicine and placed in a dynamic continuum where his operation can be more correctly viewed as only a single experience in a sea of many experiences. The gastrectomy then does not loom as something which is the end and all of everything, but rather an experience to which the patient reacts in a way for which all his past and present subjective experiences have prepared him and which will permit him to react without his having too much choice in the matter.

The surgeon looks for good postoperative results based upon his carrying out a good mechanical procedure in the operating room and during the postoperative hospital period. The results, as far as the surgeon is concerned, leave something to be desired. Dr. Robert Zollinger has a thought that the weight of the patient, his body build, may be associated with the results he obtains with his postgastrectomy patients—the thin patient being a poor risk, the heavy patient being a good risk, and the patient of medium build coming in between these two as far as postoperative results are concerned. Hypnosis postoperatively with suggestion has been recommended as a means of clearing up some of the discomforts following operation for duodenal ulcer, indicating the belief in the psychological implications in the postgastrectomy patient's complaints.

The patient material collected in this study was sorted into four groups for the purposes of analysis. The first group contains 25 patients (1 woman,

24 men). This group is made up of patients who were very much pleased with their operations and offered no gastrointestinal complaints voluntarily. The one female patient was an elderly (74-year-old) Negro woman, the only Negro in the study. The 2 patients, both men, who seemed to have developed substitutive symptoms after gastrectomy are in this group.[2, 3] One of them developed a rheumatoid type of arthritis of the hips, the other chronic nasal congestion. Both complained of these spontaneously. Also included in this group are the 2 men patients, to be described later, who showed a clearing of their postgastrectomy syndrome, when changes in their lives took place 1 to 3 years postoperatively.

The second group, made up of 15 patients (12 men and 3 women), I labeled the pleased but complaining group. These patients, although expressing satisfaction with the surgical results, voluntarily complained of various gastrointestinal disturbances. Included in this group are 2 of the 3 men patients to be described later who had the same pain after gastrectomy. One of the women patients in this group was chosen to be discussed later as someone whose ulcer was severely aggravated by an acute emotional disturbance. This patient and one of the men gave histories suggestive of serious depression when they were acutely upset by emotional experiences and suffering markedly with their ulcers.

The third group is made up of 4 patients (2 men, S. M., C. D., and 2 women, E. C., N. M.), who are grouped together as overtly anxious complainers. They expressed themselves as being pleased with the surgical results specifically as related to the ulcer discomfort, but were obviously distressed by tension. The 2 men were working at their regular occupations. The 2 women, both married, were adjusting marginally, but were still at some useful daily activity.

The fourth group consists of 6 patients (2 women, 4 men), who were not satisfied with the operation. They all had gastrointestinal complaints superimposed upon a severely emotionally ill state. Neither of the 2 women had ever been strong and both had had several operations. They both had been struggling for years to attain a state of emotional equilibrium without success. The one woman patient (W. B.) dated her first stomach trouble at the age of 8 years. She is discussed later. Of the 4 men, one (C. C.) said, "the operation took all the sap out of me," another (H. C.) was a food crank and faddist, another (V. R.) claimed his nervous system was shocked by the operations and he was now more nervous than before, and the last (D. R.) wished he could go back to his ulcer, which bled five times prior to operation, because he had been having so much discomfort since then. The second woman patient (K. D.) is a 65-year-old woman who never had pain from her ulcer. She is a very tense person and has postgastrectomy diarrhea.

Two primary factors seemed to me to be operative in these 50 cases. First, the reaction to the operation is obviously a very important factor in the over-all results. The grouping above is on this basis. It is very similar to the reaction to medical illness, where the reaction may require more attention than the illness itself.[11] These reactions, since the operation was correctly carried out, are related to the personality of the patient. Second, the importance of the

ulcer itself as a major source of discomfort seems important. Once emotional factors set up a physiologic disturbance, the disturbance itself may become additive. Thus, while a blush may result from a stressful experience, it may be added to by itself. That is, the person blushing may be embarrassed further by the blush, which then leads to a deepening of it. So also perhaps with peptic ulcer, the removal of which, if it is the primary cause of the continuing stress, leads to the best recovery possible, as exhibited by the first group of patients. The first group contained 10 patients with no dietary restrictions.

The surgeon takes on all comers, emotionally speaking, and his results are reflected in an unselective way in the lives of his patients. This study indicates that emotional factors, stressful subjective experiences, are active in an important way in the lives of the duodenal ulcer patients pre- and postoperatively.

It was noted that changes in the patient's life after operation can transform what seemed to be a poor result to a satisfactory one. Two examples of this follow:

E. E., a 70-year-old white widower, was seen 4 years after operation. This man was once a railroad brakeman. He left the railroad early in their married life, at his wife's insistence, and as he said "to keep peace in the family." He moved to a small town with her and took a job in his brother-in-law's hardware store. He worked at this job for 35 years. About one year after entering the hardware business he began going to the doctor for stomach trouble which was eventually diagnosed as duodenal ulcer. He was treated medically for this complaint for about 35 years. He retired in March of 1953 and in the following year, May, 1954, he had a subtotal gastrectomy. He had it at this time because "the pain was making me very nervous." After operation he did not do well for 3 years. Food, as he put it, "went right through me." He lost weight from 175 pounds to 111 pounds and remained at that level. Up to this point he was considered to show a poor postoperative result. The patient's wife developed cancer and died in June, 1957. Within the week of her burial he entered the hospital and had a gangrenous great toe removed by the same surgeon who had performed his gastrectomy. The patient had suffered from his toe disturbance approximately 6 weeks. Immediately he began to feel better, began to eat better, and to be able to retain his food. Today, at the time of this study, this man weighs 165 pounds, up 50 plus pounds from his previous low. He now lives alone, does his own cooking, and has very little bowel discomfort. He is quite content to pass his time alone in his small home or at fishing.

D. H., a 26-year-old white married man, is another example of postoperative environmental changes bringing about a good result post gastrectomy where previously the result had been considered as poor. This man, when seen, was 2½ years post gastrectomy. At the time of the interview he stated that he felt very well. He said, however, that he did not begin to feel as well as he does now until one year after operation. In the immediate postoperative period he had a pain of a type similar to the pain he had prior to the operation although he had no recurrence of the duodenal ulcer. This patient was operated on while he was in college. He was married in December of 1954, was operated upon in November of 1955, and had a daughter born to him in February, 1957. He was graduated from college in June of 1957. Graduation from college coincides with the beginning of his present excellent physical state. He stated that school was extremely difficult for him and that he finished up and graduated only through sheer tenacity. He said school was hard on his nerves. It "pried on my mind" all the time. He would worry about examinations weeks before he took them. Since he is out of school he says he has no worries whatsoever. He is a sales representative for a large oil company and is doing quite well in business.

He is a big man physically and an ex-Marine enlisted man. He lives with his wife and young daughter. He does not go to the doctor any more, is very pleased with the results of his operation, and says he can take things easier since then.

This patient was on the bottle at bedtime until he was 5 years old. His mother died when he was about 9 years old. He first noticed the onset of his ulcer pain when he was about 20 years old when he had returned from Korea where he had been serving with the Marine Corps. He was able to serve out his full 3-year period of enlistment and received a nonmedical honorary discharge. His ulcer symptoms began upon his return from Korea, in a period when he was drinking alcohol heavily. He uses no alcohol now.

The ulcer history of these men is wrapped up with the story of their adult lives.[7] The 70-year-old man (E.E.) was operated upon after his retirement, and the stressful upsetting aspects of this have been pointed out very clearly by Tyhurst.[14] The onset of his present improved state relates closely to the death of his wife.[16] He had an amputation of a toe within the week of his wife's burial. The significance of this procedure to the patient is not clear. In the case of D. H., the 26-year-old man, we find again changes in subjective experiences being associated with, first of all, changes in his digestive processes and the appearance of ulcer pain, and, second, the disappearance of postoperative symptoms with the cessation of significant stress. Without any attempt to establish a one-to-one direct cause-and-effect relationship here, a fluctuation of experiential dynamic factors can be seen to be reflected in the postgastrectomy patient's postoperative condition.

Changes in the homeostatic balance of the patient's life can also lead him to surgery. This is rather dramatically illustrated by another case:

C. M., a 40-year-old white man, separated from his wife, was seen one year after operation. He worked as a roofer in various towns around central Ohio. He was married in 1943 and had two children. He first had severe pain in his stomach at the age of 12 years. This pain would double him over. He remained in the army only 10 months and was discharged because severe abdominal pain incapacitated him for duty. He was a somewhat irresponsible irregular worker and drank alcohol to excess. He says he drank especially heavily on weekends, and away from home at bars, to ease his pain. He and his wife had been making a poor adjustment for several years. He said, "She would call me an S.O.B., 7 to 8 hours at a time." He had been advised on many occasions by his local doctor to have gastric surgery for a proved duodenal ulcer. He had declined to do so for many years.

He returned home one Friday afternoon after having worked out of town all week to find all the furniture moved out of his apartment. His wife and children had gone. His wife told him later, when he found her, that she was not coming back and that she was going to get a divorce. He was admitted 2 weeks from the fateful Friday, after telling his wife he was entering the University Hospital for operation on his stomach. When he told her he was going to be operated upon, she accused him of doing it to obtain her sympathy.

This patient, when interviewed, was in the hospital, 16 months post operation. He was there for surgical evaluation of pain. Nothing was found to be out of order. He was found not to have a recurrent ulcer. He was complaining of the same pain as before operation. He was noted to be a rather silly fellow. He complained of the pain while I was interviewing him, yet showed no facial evidence of pain. He claimed that for 3 months after his gastrectomy he could not keep much food down and would vomit two to three times a day. This cleared, his appetite was good for awhile, he "ate like a horse." Then 6 months after the operation the pain returned while he was away from his home town working. He quit working at this time and has been unemployed since. He moved in with his elderly mother and father. He has been living on unemployment compensation, "rocking chair money," he

says. His is a case of extremely mild dumping. He can eat almost anything without bad effect. He has pain in the epigastrium all the time. He said during the interview that prior to operation "the floor looked slanting." He said the operation had cleared this up for him. This patient had a brother who was operated upon for duodenal ulcer, 4 to 5 years prior to the patient. This brother also had a return of the same pain. This patient has successfully interfered with his wife's effort to obtain a legal divorce. He wants her back. She refuses to have anything more to do with him.

This man appeared to be an emotionally unstable fellow who was discharged from the army after 10 months on a character disorder discharge as being unadaptable. One wonders how long he would have gone before entering for surgery if his wife had not left him when she did. This forced separation from his wife upset the dynamic balance he had tenuously established between himself and the environment. This patient's adjustment with the environment is still out of alignment as evidenced by the presence of the same type of pain that was present prior to operation. One might say that this pain plays a role in maintaining perhaps whatever stability he has left. One wonders what favorable experiences, if any, this man will have to have in the future in order to have his present unsatisfactory postgastrectomy state modified to one that can be considered good.

The operation was a mechanical success, but it has not relieved or aided his dynamic balance with his environment. The surgeon is at a loss to find any way of helping this particular type of patient. Perhaps psychiatry in the not-too-distant future can find some method of helping the surgeon with this particular problem. Perhaps if it had been known how this man came to surgery at the time he did, there might have been hesitation to operate upon him because of the evidence of a developing imbalance of a more serious nature in his personality adjustment.

The above-mentioned patient, C. M., was one of 3 patients, all men, who complained of the same type of pain after operation as before. The second such patient was a 34-year-old white married man who received a Veterans Administration pension because his ulcer was diagnosed in the service. He seemed rather sheepish when Dr. Zollinger questioned him about his pain. He apparently needed it for the compensation it gave him. It was not incapacitating him for work. The third patient was a 36-year-old white married man. He was a small, thin, nervous, worrisome person. He was not at all satisfied with the results of his surgery. He said, "If I could, I would go back to my ulcer." After eating he will have pain in the epigastrium and chest. Every night about 2:00 A.M. he has a hot regurgitation in his mouth. He has pain in the middle of the abdomen and around both sides to the back. "One horrible thing after another." His local doctor says he has spasms in the esophagus and stomach. He had his first stomach trouble in his third year in high school. He was in the army in 1941-1942 for 11 months. He was discharged because of abdominal pain and without a diagnosis of peptic ulcer. He had five hemorrhages from December, 1942, to October, 1954. Surgery had been recommended in 1951 by his family doctor. He said he put it off because, "I like everyone else feared the operation." He said he knew of one fellow who bled to death at operation. He does not know how to relax, even on a vacation—a chronically anxious man who put off surgery in the face of five serious hemorrhages because of fear. He says

he is as grumpy and miserable since operation as before but he does not miss any work because of his abdominal discomfort. He has to eat slowly or he will vomit. He has the dumping syndrome to a considerable degree. Since the operation, 3½ years ago, has not been productive of comfort, one might conclude that it was a failure. However, it would seem more accurate to say that the operative procedure was just another experience for this man which failed to modify his environment favorably to a significant degree. Although it was a mechanical success, he continues to react unfavorably to subjective life experience.

There were no clear-cut cases in which duodenal ulcer could be said to have begun as a result of the imbalance of dynamic forces operative in these patient's lives. Many patients gave histories which indicated that the upsetting of their dynamic environmental balance contributed to an aggravated ulcer state. Two examples of this are seen in the following cases.

E. J., a 60-year-old white widow, was 4 years past operation. She was separated from her husband in 1950, and they were divorced in 1953. She had one child, a son. She stated in her history that this son was killed at the age of 33 in 1952, in an air crash. At that time he was a Major in the Air Force. She said, "This is when my ulcer went haywire and they couldn't heal it." She could not keep anything on her stomach and a complete obstruction finally developed. She stated that she had been getting along fairly well prior to that time. Her physical course was progressively downhill from the time her son was killed on Nov. 22, 1952, until she was operated upon in May of 1954. She had lost considerable weight and had not been eating well for quite a while. She had become very weak, and had been too ill to work for almost one year prior to operation. This case emphasizes the apparent accumulative effect of stress and the progressively developing dynamic imbalance.

Another example of a patient who verbalized the upsetting factors in her life as they related to the aggravation of her ulcer symptoms was K. D., a 65-year-old white widow. She had been a widow since 1937 and had been working as a buyer in a department store in a medium-sized city in central Ohio. She was 22 months postoperative at the time of this study. Her hemigastrectomy was her third surgical procedure in a 2-year period.

After her husband's death the patient worked and lived with her mother who had worked outside the home for about 27 years. Finally the elderly mother could no longer work, and then at the age of 81 had to be committed to a state hospital for the mentally ill. The patient felt considerable anxiety at having to commit her mother to a state hospital. She said it was a terrible place, she was broken up every time she came back from a visit with her mother. She expressed guilt that she had to put her mother in there because she ran away from home. She said that, every time she went to visit her mother and talk to the doctors about her, her mother was put into worse quarters. She dates the onset of her severe ulcer symptoms to the time when her mother entered the state hospital. The mother died in the state hospital in April of 1954 and the patient had her first operation, an exploratory one for the source of intestinal hemorrhage, in July of 1954, about 2 months after the mother's death.

The patient was an only child. She stated that she had always been nervous and high strung. She had not worked since her first operation in 1954. She has almost chronic diarrhea postoperatively which she can keep somewhat under control with a daily dose of bismuth or paregoric.

Early age at onset of abdominal pain may indicate a poor prognosis. Many patients with poor results gave this history. The earliest memory of age of onset of severe abdominal pain was from one of the women patients seen in this study.

This patient was one of the more, if not the most, emotionally unstable persons evaluated.[5, 8, 9, 13] Her first episode of abdominal pain occurred at the age of 8 years. She recalled that she rolled on the ground in pain. This seems to have occurred the day they received news of her father being injured in an "oil field" accident, after which he was an invalid and never walked again. She had been eating green apples in the orchard that day. This patient was a 37-year-old white married woman. She appeared extremely cachectic (weight 87 pounds), and much older than her stated age. She had a gridiron abdomen, the result of many previous surgical operations. She had had intermittent abdominal pain from the age of 8 until 21 years. She was treated for it without relief. This pain became constant "right after I was married." She married a big 6 foot, 2 inch, dark-haired, pleasant-appearing man who is a "pumper in an oil field." She was never able to bear a child. In fact, she denied ever having enjoyed sexual relationships. She put up with them because her husband was such a wonderful person. She and her husband adopted a daughter who at the time of this study was 11 years old and had already had three operations for a congenital knee difficulty.

This patient is an individual who had never been able to meet life's ordinary stresses adequately, although it seemed to me she had wanted to do so.[4, 10, 15] At this time she is unable to gain strength because she has frequent loose stools, poor appetite, and occasional abdominal pain after eating. The surgeon was a brave man to take on such a patient. She had little emotional strength before the operation. The gastrectomy was not an ego-strengthening procedure. She still seems to be chasing the will-o-the-wisp of physical health, which she seems unlikely ever to obtain because of her personality weakness. Her case could not in any way be considered an operative success. She has a severe dumping syndrome. Surgically the mechanical result was good. She had had her bowel disconnected and reconnected many times successfully. The gastric operation had removed the ulcer. To expect more of it than removal of the ulcer seems unjustified. The ulcer was not the "cause célèbre" of her complaints, but only one of a number of distressing symptoms seemingly related to her inability to meet the ordinary stresses of life which secondarily kept her in a chronic state of imbalance.

SUMMARY

Fifty postgastrectomy patients were seen for psychiatric evaluation. Their subjective experiences and the part they play in the peptic ulcer patient's life are discussed and evaluated. The results of the study are ordered to the theory of dynamic interpersonal and intrapersonal balance, as the field of operation in which to make such observations. The surgical operation is thus seen in a different, more realistic position, as is the patient's response. The patients are divided into four groups, with only one group (6 patients, 12 per cent) expressing dissatisfaction with the operative results. The other three groups (44 patients, 88 per cent) expressed satisfaction with the operative results, even though some had complaints. Various individual patients are discussed to point out certain important observations of the study.

CONCLUSIONS

Emotional factors play a vital part in the duodenal ulcer patient's symptoms before and after operation. They play a role in the aggravation of ulcer symptoms, in the production of the dumping syndrome, in the complaint of pain postoperatively, and in the bringing of the patient to surgery.

The early age at onset of abdominal pain in a patient who comes to operation for duodenal ulcer may bear an inverse relationship to the successful outcome of gastrectomy and vagotomy, because of associated emotional factors.

When the surgical procedure is carried out as reported in this study, the results are very closely tied to the state of emotional balance present in the patient at the time. If the ulcer is the primary stress factor, in a stable personality its removal leads to excellent results postoperatively. When the ulcer itself, which is the chief cause of the complaint (self-perpetuating), is removed surgically, recovery occurs. If, however, the ulcer is associated with an emotionally unstable personality, nothing but poor results can be expected. Finally, where the personality balance is not completely inadequate, and the ulcer is not the chief source of stress, varied results occur. This is the group in which predictability varies. Here one finds the postgastrectomy syndrome, with or without complaint. In this group one also finds the postgastrectomy syndrome clearing, with later emotional changes of a significant degree.

Further more intensive psychiatric study is needed of the postgastrectomy, dumping, or postprandial syndrome in relationship to emotional factors.

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FLUID ABSORPTION FROM THE SMALL INTESTINES

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KNOWLEDGE of factors regulating the absorption of fluid and ions from the gastrointestinal tract would be of value in planning a therapeutic regime in patients with excessive losses of gastrointestinal fluid. We have noted that some drugs cause alterations in the amount of ileostomy drainage. Physiologic information on the hormonal control of gastrointestinal absorption is necessary before any inquiry into drug control is undertaken. The similarity between the transport of fluid and electrolyte by the renal tubule and the intestinal mucosa has been suggested by the work of Visscher and associates,[8, 9] Lifson,[4] Wertheimer,[5, 10] and others.[3] For example, phlorizin interferes with sugar absorption from the tubules; it also inhibits active sugar absorption in the intestine.[10] The marked decrease in sodium chloride absorption from the small bowel of rats after adrenalectony shows further evidence of the similarity between renal and intestinal absorption. An attempt was made to study the action on intestinal fluid exchange of agents known to affect renal function.

MATERIAL AND METHODS

Four adult mongrel dogs were prepared with a modified Thiry fistula in the following manner: With the dog under pentobarbital anesthesia, a vertical midline incision was made extending from the xyphoid to the level of the iliac crest. The ileum and cecum were delivered into the wound. An intestinal clamp was placed across the ileum 10 cm. proximal to the ileocecal valve and another clamp was placed 40 cm. proximal to the first clamp. The bowel was severed at the level of these clamps and the mesentery carefully freed from the adjacent mesentery to preserve the blood supply to the isolated loop. The proximal and distal free ends of ileum were anastomosed by the open technique to restore continuity to the gastrointestinal tract (Fig. 1). The distal end of the isolated loop was closed by the method of Parker and Kerr. The proximal end was brought through the abdominal wall in the right lower quadrant. An antiperistaltic pouch was necessary to prevent fluid leakage. The ileostomy was fashioned by everting the mucosa as described by Dennis (Fig. 2). The abdominal wall was closed in layers.

The animals were allowed to recover for 2 weeks. They were trained to lie quietly on a specially constructed dog board while their loops were gently irrigated with saline. After one week of such training the experiments were

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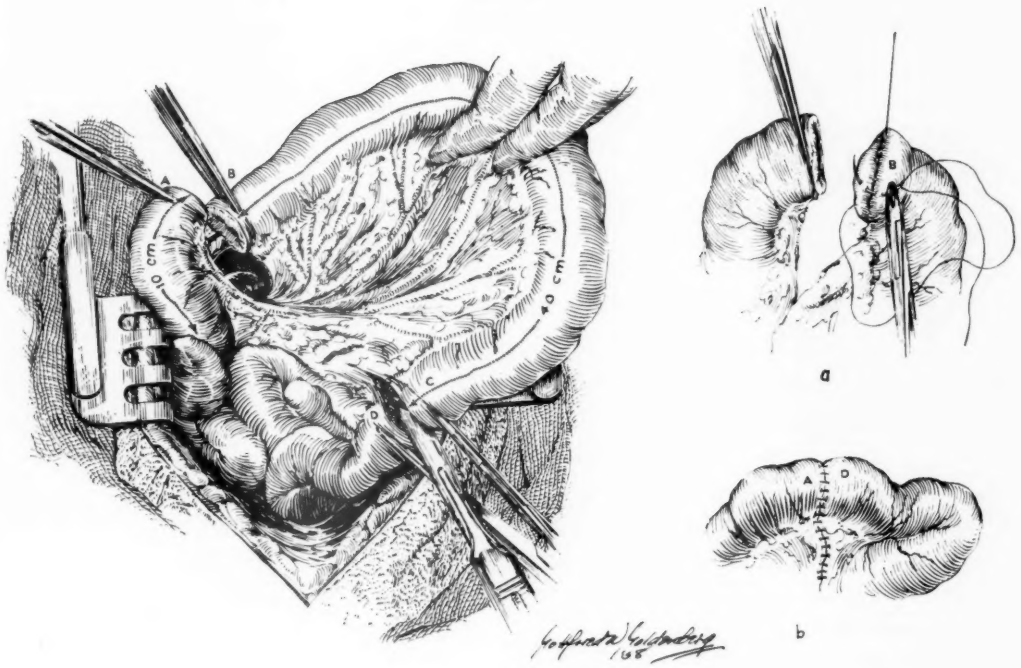
Fig. 1.



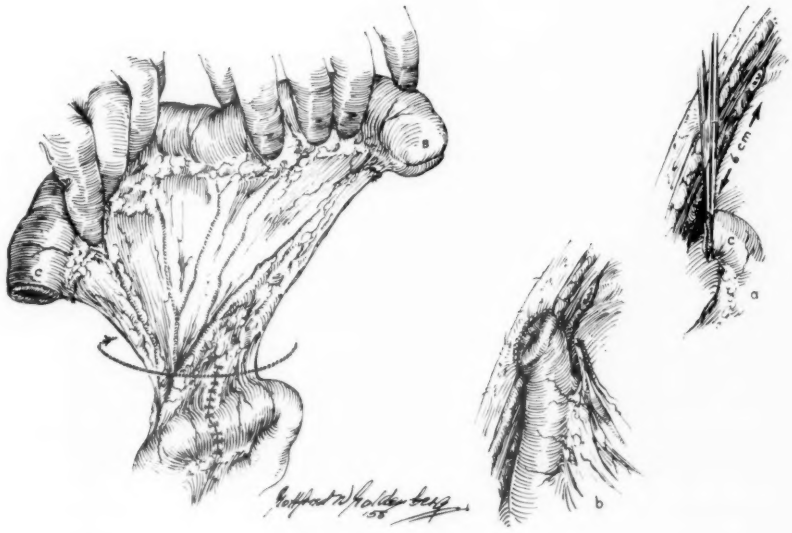


Fig. 2.

Fig. 1.—The terminal ileum is divided 10 cm. from the ileocecal valve. A loop of ileum 40 cm. in length is secured and division made proximally. Intestinal continuity is restored. The distal end of the loop is inverted.

Fig. 2.—The isolated loop and its mesentery are shown. The manner of bringing the open end of the loop through the abdominal wall is demonstrated.

begun. A No. 20 catheter was introduced into the pouch. The pouch was irrigated three times with 50 c.c. of saline. The irrigating fluid was aspirated after which 50 c.c. of saline was introduced. The dog remained on the board for 30 minutes at which time the fluid remaining in the loop was aspirated and measured. This procedure was repeated daily on each animal for five consecutive trials. The mean value of fluid absorbed was used as a control for each dog.

The same method was employed one hour following ingestion of 30 c.c. of absolute alcohol in 120 c.c. of water. The mean value of fluid absorbed in 30 minutes was calculated.

After a 5-day rest, each animal was given intramuscular Pitressin (0.1 μ per kilogram of body weight). After a 10-minute interval, absorption was measured as before. This latent period was decided upon after determination that the maximal effect of Pitressin occurred within an hour.

In a final series, absorption was measured 3 hours following intramuscular hydrocortisone (10 mg.). Again, this interval was used because maximal effect was manifest between 3 and 4 hours following injection.

RESULTS

The results of 5 experiments on each animal are averaged in Table I. There is a significant difference between the control absorption and the absorption of

TABLE I. THE AVERAGE ABSORPTION IN 5 DIFFERENT EXPERIMENTS ON 4 DIFFERENT DOGS. PITRESSIN ENHANCES WATER ABSORPTION WHILE ALCOHOL AND CORTISONE RETARD IT

DOG NO.	ABSORPTION (CONTROL) C.C./MINUTE	ABSORPTION 1 HOUR POST ALCOHOL*	ABSORPTION 10 MINUTES POST PITRESSIN†	ABSORPTION 3 HOURS POST CORTISONE‡
1	1.34	0.63	2.10	1.0
2	0.27	0.11	0.38	0.17
3	0.97	0.38	1.50	0.40
4	0.45	0.17	0.61	0.24
Average	0.76	0.32	1.15	0.45

*Thirty cubic centimeters 97 per cent alcohol in 120 c.c. distilled water.
†Pitressin 0.1 unit per kilogram intramuscularly.
‡Hydrocortisone 10 mg. intramuscularly.

saline under the influence of the three agents tested. Results are expressed in cubic centimeters per minute although evidence for a linear rate is not too clear. Dennis and Visscher[1] in studies under similar conditions found that there is a linear progress of absorption until 50 per cent of the fluid has disappeared. In the pre-experimental phase, it was noted that absorption was erratic when the dog was emotionally upset, a factor which will be studied later. This problem was overcome by the extensive training phase[2] after which the variation for any individual experiment was minimal. These investigations have disclosed that agents affecting renal water balance act on intestinal fluid absorption in a predictable manner. Agents causing diuresis will inhibit absorption of fluid from the intestinal loop while antidiuretic hormone will enhance intestinal absorption.

DISCUSSION

The diuretic action of alcohol has long been appreciated by laymen (Shakespeare, Macbeth, Act. 2, Scene III). The mechanism by which alcohol produces diuresis is to inhibit the release of posterior pituitary diuretic hormone. van Dyke and Ames[6] have shown that alcohol does not produce diuresis in dogs with diabetes insipidus and that the diuretic dose is much less by the intracarotid than by the intravenous route.

The posterior pituitary hormone exerts its antidiuretic action directly on the renal cell.[7] It enhances water absorption from the distal tubule to produce urine of higher osmolarity than that of the blood. In basic terms, its main function is to produce a positive water balance. Its action on intestinal water absorption, as shown by this experiment, is consistent with this thesis. By reducing the secretion of posterior pituitary hormone, alcohol acts to produce a negative water balance and inhibits intestinal fluid absorption.

The mechanism by which the adrenal steroids act to produce a negative water balance is less well understood. Much experimental evidence shows that there is an antagonism in action on water metabolism between the antidiuretic hormone and the adrenal steroids.[3] The steroid hormones inhibit water absorption from the distal tubules while ADH enhances it. After adrenalectomy animals have difficulty in excreting a water load. Large doses of cortisone in experimental animals lead to polyuria and polydipsia (false diabetes insipidus). Our experiments show the effect of hormones on water movement from the gastrointestinal tract to be equivalent to the effect on water movement in the distal renal tubules.

There are many clinical applications of this thesis. The control of fluid loss through an ileostomy by avoidance of alcohol seems reasonable and has been advised empirically for several years. The effects of hypertonic saline and forced fluid restriction, both excellent antidiuretic mechanisms, are being investigated as methods of reducing ileostomy drainage.

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SERUM AMYLASE LEVELS IN EXPERIMENTAL INTESTINAL OBSTRUCTION

Observation of the Amylase Activity of Abdominal Fluid In Dogs With Complete Small Bowel Obstruction

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SINCE Elman[6-8] described the elevated amylase activity in the serum of patients with pancreatitis, it has been found that an elevated serum amylase level is usually indisputable proof of acute pancreatitis. It is becoming more apparent, however, that it may be elevated in other diseases such as mumps,[1, 17] cerebral trauma,[22] administration of opiates,[2, 10, 16, 19] and renal insufficiency.[13, 20]

Of particular interest is the occasional finding of high amylase levels in cases of perforated ulcer where the mechanism is thought to be the escape of the gastroduodenal contents into the free peritoneal cavity with the amylase being rapidly absorbed into the blood stream.[15, 18]

We have shown in a previous study[4] that dogs with complete mechanical small bowel obstruction, either high or low, who eat and vomit, have a rise in serum amylase activity. This rise, which may occasionally be of the same magnitude as that seen in experimental pancreatitis, has been previously found by Burnett and Ness[3] in cases of intestinal obstruction in human beings. It appeared from our earlier studies that an intact, obstructed duodenopancreatic segment was necessary for the elevation of the serum amylase, since this elevation did not occur in Mann-Williamson[12] preparations where intestinal obstruction was produced proximal to the duodenoileal anastomosis.

It has been suggested[5, 14] that the rise in serum amylase activity might be due to transudation of intestinal amylase through the obstructed, partially devitalized intestinal wall into the peritoneal cavity and thence directly to the blood stream as in the perforated gastroduodenal lesions. In order to investigate the possibility of this transudation, a study of both the serum and abdominal fluid amylase in complete mechanical small bowel obstruction in dogs was carried out.

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METHODS

Thirty-five adult male and female dogs weighing between 8 and 20 kilograms were used. Twenty-one were acceptable for study. The others were excluded because of death from anesthesia, death from pneumonia, and very early postoperative deaths due to suture-line leaks or blood loss.

Serum amylase values were determined by the method of Somogyi[24] which makes use of the well-known Wohlgemuth starch-iodine color reaction, and its timed disappearance. Normal levels of serum amylase in the laboratory[4] varied from 800 to 4,000 units. The serum amylase in dogs is approximately ten times that in the human.[21, 23, 25]

All operations were performed under intravenous pentobarbital (Nembutal) anesthesia. Occasionally an endotracheal tube was inserted, and an Emerson respirator was used to deliver oxygen and maintain respiratory activity in apneic dogs. In all cases the intestinal obstruction was produced by complete transection of the small bowel at the selected level. Each severed end was inverted with two layers of running chromic catgut and reinforced with a single layer of interrupted silk sutures. The ends were then basted together to prevent intussusception of the distal end, which was the cause of death in 3 dogs early in the series.

Mann-Williamson[12] procedures were performed in much the same way. The blind proximal duodenal end was closed with two layers of running chromic catgut sutures and a single layer of interrupted silk sutures. The proximal jejunum was sutured to the distal stomach with an inner layer of inverting continuous chromic catgut and an outer layer of interrupted silk. The distal end of the duodenal loop was anastomosed end-to-side to the terminal ileum 3 to 5 cm. from the ileocecal junction in an identical fashion. Following this procedure the dogs were not fed for one week, but were maintained with parenteral fluids and electrolytes as well as daily parenteral procaine penicillin and dihydrostreptomycin. After this 7-day period, they were slowly brought back to a routine kennel diet over a period of 3 to 5 days.

In dogs which received parenteral fluids, the fluid in general consisted of 5 per cent dextrose in 0.85 per cent saline, and was administered in 300 to 500 ml. amounts depending on the size and condition of the dog. The fluid always was given in the form of a "push" hypodermoclysis in the interscapular area, and 150 turbidity-reducing units of hyaluronidase were added to each clysis. The fluid always was absorbed within 2 hours. No infections of the area were observed.

All dogs studied were subjected to abdominal paracentesis daily at the time of the drawing of one of the blood samples (some dogs had blood samples drawn more than once every 24 hours). The paracentesis was carried out with a clean, dry, sterile syringe and a No. 18 gauge, short-bevel, 1½-inch needle. During the course of this large series of abdominal taps, the bowel was entered on several occasions as was the bladder. The characteristic odor and consistency of the contents of each of these organs left no doubt as to

the location of the aspirating needle. That such an unsought location may be found by the needle must be recognized in both the dog and man. The amylase content of the small bowel is high in both species; the amylase activity of dog's urine is zero under all conditions, and that of human urine is low in most instances. It seems obvious, in retrospect, that in the case reported from the Massachusetts General Hospital[5] the small bowel was entered by the aspirating needle, and that the high level of amylase activity reported for the abdominal fluid was in reality the activity of the contents of the small bowel. This source of error must always be kept in mind. In all instances in this series of dogs, when either the bowel or the bladder was entered, there were no complications. The needle was withdrawn quickly from the abdomen. The needle and syringe were discarded and a fresh sterile set was used to reaspirate the peritoneal cavity immediately.

In certain of the animals with intestinal obstruction, no abdominal fluid could be obtained, and at necropsy these dogs were found to have no peritoneal fluid.

Sections of the pancreas were taken from each animal at autopsy shortly after, or at, the time of death. Sections were stained with hematoxylin and eosin, and studied by Dr. William Freeman of the Department of Pathology, and were graded for the presence or absence of changes consistent with pancreatitis after the method of Lium and Maddock.[11] These studies will be reported elsewhere.[9]

RESULTS

In 5 dogs the obstruction was placed in the high jejunum. They were fed the routine diet, but were given no parenteral fluids (Fig. 1). Dog A developed no abdominal fluid, yet the serum amylase rose. Dog B on two occasions and Dogs C and D each on one occasion had free abdominal fluid present, but never did its amylase content exceed that of the serum drawn simultaneously. The serum amylase rose in Dogs A, C, and D and was related to the onset of vomiting. Dog B ate and vomited but for an unknown reason the serum amylase did not rise. Dog E on two occasions had abdominal fluid amylase values which exceeded the amylase content of the simultaneously drawn serum. At autopsy this dog was found to have a frank intestinal perforation at the suture line with gross peritonitis.

In 5 dogs the obstruction was in the terminal ileum. They were fed the routine diet. No parenteral fluids were given (Fig. 2). Dog A developed no abdominal fluid yet the serum amylase rose. Dogs B and C had abdominal fluid present, but the amylase activity never exceeded that of the serum drawn at the same time. The serum amylase levels of these 3 dogs rose with the onset of vomiting. Dogs D and E lived too short a time after operation for vomiting to begin. Dog E was the only dog of this group that had an abdominal fluid specimen with a higher amylase activity than that of the concomitant serum specimen. At autopsy this dog had a suture line leak with gross peritonitis similar to that of Dog E of the high obstruction group.

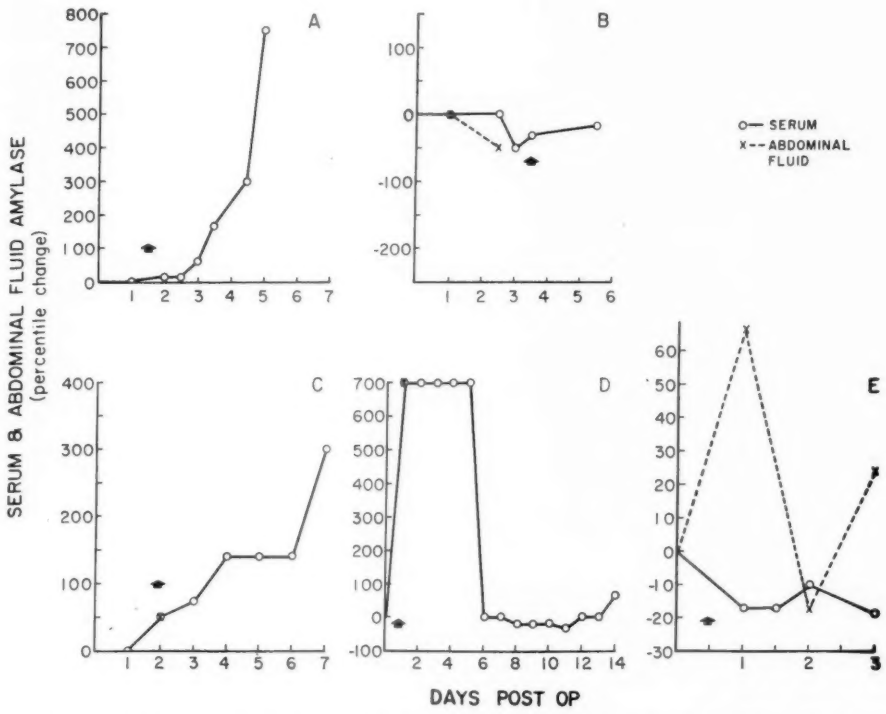

Fig. 1.—Serum and abdominal fluid amylase activity in high obstruction when dogs were fed, but received no fluids parenterally (vomiting and dehydration). The arrow (↑) indicates the onset of vomiting.

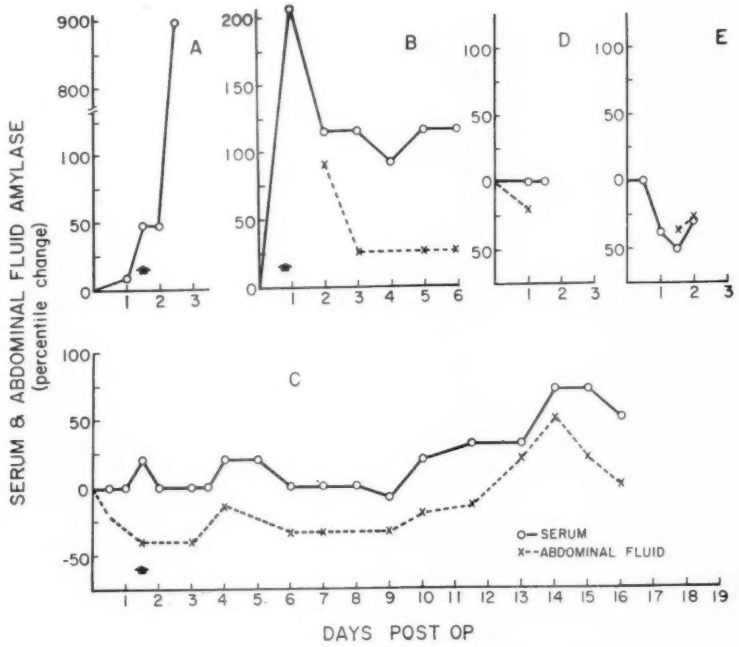

Fig. 2.—Serum and abdominal fluid amylase activity in low obstruction when dogs were fed, but received no fluids parenterally (vomiting and dehydration). The arrow (↑) indicates the onset of vomiting.

Fig. 3 shows the results of a study of 4 dogs with obstructions in the terminal ileum, which were allowed to eat and vomit, but were given parenteral fluids and electrolytes. Dog A developed no abdominal fluid, but the serum amylase rose with vomiting. Dogs B, C, and D developed abdominal fluid, but at no time did the amylase content of the abdominal fluid exceed the serum amylase value. This is somewhat surprising in the case of Dog D, as this specimen died of a suture line leak and peritonitis.

Fig. 4 represents a group of 3 dogs treated similarly to those of the last group, with the exception that the obstruction was created in the high jejunum. Dog A developed no abdominal fluid, but the serum amylase rose abruptly with the onset of vomiting. Both Dogs B and C developed abdominal fluid, but on each occasion its amylase activity was less than that of the serum drawn concomitantly.

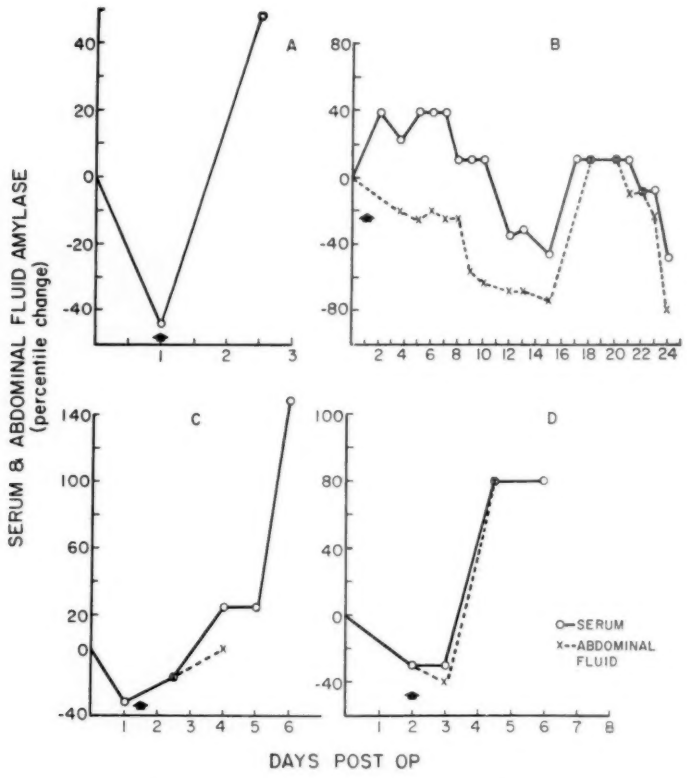

Fig. 3.—Serum and abdominal fluid amylase activity in low obstruction when dogs were fed and given fluids and electrolytes parenterally (vomiting with no dehydration). The arrow (↑) indicates the onset of vomiting.

The final group of animals were prepared by the Mann-Williamson[12] procedure, which allowed the duodenal, biliary, and pancreatic secretions to drain into the terminal ileum. Two to 3 weeks after the original operation obstruction was created in the terminal ileum proximal to the duodenoileal anastomosis (Fig. 5). The animals were allowed to eat and vomit, and were given parenteral fluids and electrolytes. All dogs developed abdominal fluid. Dogs A and B had slight or no increase in the serum amylase concentration

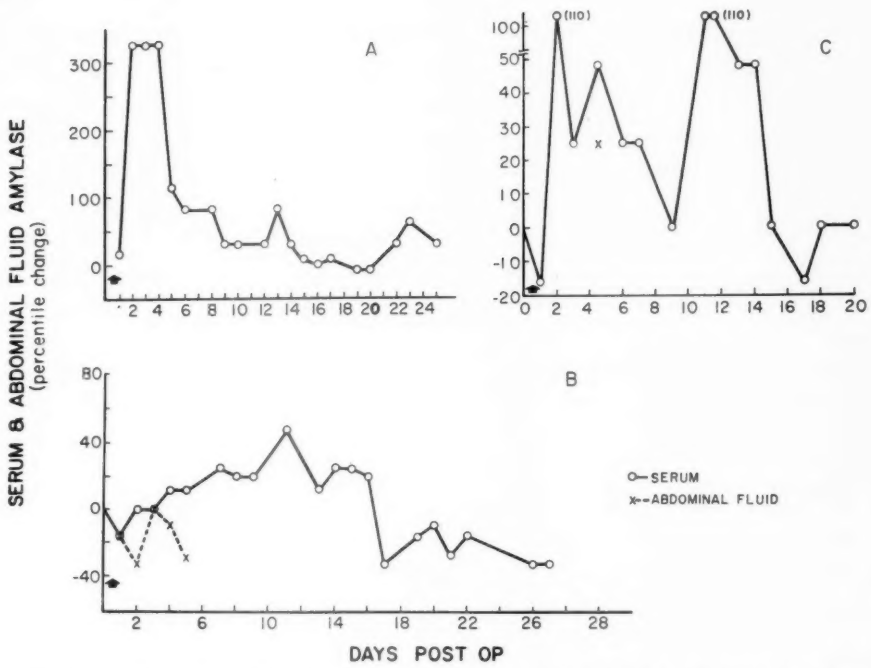

Fig. 4.—Serum and abdominal fluid amylase activity in high obstruction when dogs were fed and given fluids and electrolytes parenterally (vomiting with no dehydration). The arrow (↑) indicates the onset of vomiting.

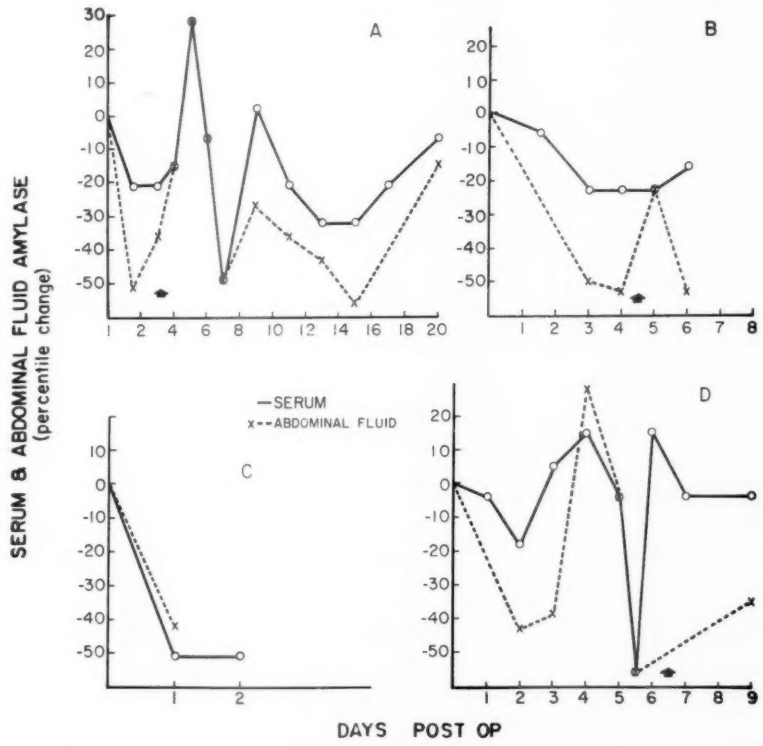

Fig. 5.—Serum and abdominal fluid amylase activity in dogs prepared by the Mann-Williamson procedure, which were fed and given fluids and electrolytes after obstruction had been created in the low ileum (vomiting with duodenal exclusion and no dehydration). The arrow (↑) indicates the onset of vomiting.

with the onset of vomiting. The abdominal fluid amylase value was always lower than that of the simultaneously drawn serum. The enzymatic response in Dog C is similar to that of dogs in the previous groups that died of a perforated bowel. At autopsy there was a perforation and peritonitis was the cause of death. Dog D had an elevation of the abdominal fluid amylase above that of the serum on the fifth postoperative day. This dog at autopsy had a perforation of the jejunum due to peptic ulceration just distal to the gastrojejunal suture line.

DISCUSSION

Intestinal obstruction was created in these animals for two reasons. The first was to substantiate the fact that the amylase activity of the serum rises in dogs with an intact gastrojejunal segment that are allowed to eat and vomit. This is amply proved by the dogs shown in the first four figures. All dogs with the exception of one (Dog B in Fig. 1), which lived a sufficient length of time after vomiting began, had a rise in the serum amylase which seemed to be related to the onset of vomiting.

Conversely, in the Mann-Williamson dogs (Fig. 5), in which the obstruction was created in such a position that the duodenal loop could not be distended by the intestinal obstruction, there was no significant rise in the serum amylase with the onset of vomiting.

The other reason for this study was an attempt to delineate further the anatomic route of the enzyme from the pancreas or gut to the blood stream. It appears that transudation can be ruled out for two reasons: (1) No free abdominal fluid was present in many of the dogs whose serum amylase rose remarkably (for example, Dog A of Fig. 1, Dog A of Fig. 2, Dog A of Fig. 3, Dog A of Fig. 4); (2) in all the dogs with an intact intestinal tract, although abdominal fluid often accumulated, there was no animal whose abdominal fluid amylase activity exceeded that of the serum drawn at the same time.

The most important group of animals in the study, however, is that group which had a level of amylase in the abdominal fluid exceeding that in the simultaneously drawn serum (Dog E of Fig. 1, Dog E of Fig. 2, Dogs C and D of Fig. 5). Each of these dogs had a perforation of the gastrointestinal tract with outpouring of the intestinal contents into the abdominal cavity. The perforation was due either to a leak at the suture line, or in the Mann-Williamson dog to a perforated jejunal ulcer. In none of these dogs was the serum amylase markedly elevated. The rise if it did occur was never of the same magnitude as it was in the dogs which developed no abdominal fluid. This furnishes further proof that transudation is not a factor producing elevation of the serum amylase in simple complete mechanical small bowel obstruction in dogs.

This finding has not heretofore been adapted to the differential diagnosis of the acute abdominal crisis in man. A study of cases of intestinal obstruction in humans is now underway to determine the validity of this observation

as applied to them. It may well be that whenever the abdominal fluid amylase activity exceeds that of the simultaneously drawn serum, a perforated intestine is the cause.

SUMMARY

The amylase activity of the serum is increased in dogs with complete mechanical small bowel obstruction that are allowed to eat and vomit. This occurs whether the obstruction is high or low and whether or not the dogs are maintained with parenteral fluids and electrolytes.

This elevation of the serum amylase is not due to an increase in the amylase content of the abdominal fluid which intestinal obstruction may produce. The serum amylase may rise when no free abdominal fluid is present. Furthermore, when abdominal fluid does form because of intestinal obstruction, its amylase activity is never greater than that of the serum drawn simultaneously so long as intestinal continuity is maintained.

In dogs with complete mechanical small bowel obstruction that have formed abdominal fluid, if the amylase concentration of the fluid is higher than that of the concomitantly drawn serum, there is always a perforation of the gastrointestinal tract. If such a relationship exists in cases of human intestinal obstruction, a valuable diagnostic aid will have been found.

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EXPERIMENTALLY PRODUCED CLOSED LOOP INTESTINAL OBSTRUCTION IN DOGS

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INTRODUCTION

DURING the past 50 years, the search for the cause of death in intestinal obstruction has been an intensive one. Certain facts have emerged from the experimental work on various types of obstruction, which have served to clarify the physiopathologic mechanisms involved. However, despite the adherence of various groups of investigators to one of several theories for the lethal factor in obstruction, the fact irrevocably remains that the picture of a fulminating toxemia accounts for the majority of fatalities of intestinal obstruction.

A number of theories concerning the causes for the ultimately lethal course of the closed loop have been advanced. These include: (1) absorption of toxin, (2) mechanical effect of obstruction, (3) bacterial absorption, and (4) perversion of physiologic secretions. Markowitz[1] believed that in high obstructions of the small intestine, toxins are produced and absorbed through a damaged intestinal wall. Wangensteen,[2] in keeping with the theory of mechanical effect due to obstruction, found that an increase in intraluminal pressure occurred, which led directly to venous stasis, impaired viability, and increased permeability of the intestinal wall. Ellis[3] also contributed to the theory of autointoxication by the observance of toxins in the distal loop of bowel after injection of toxins into the proximal segment. He also commented on Kocher's finding that washing the loops in experimental animals prolonged their life.

Evidence for the bacterial theory as a lethal factor in intestinal obstruction is quite convincing. Harper and Blaine[1] found that penicillin placed in closed loops afforded protection to 60 per cent of experimental animals for one month and to 90 per cent for 2 weeks. This was further substantiated by their finding that a high bacterial count was compatible with life, providing the loops were aspirated. Nemir and associates[4] also adhered to the theory of bacterial intoxication. They produced strangulating obstruction in dogs and corroborated Harper and Blaine's finding of the improvement in the toxemia by the use of antibiotics. They believed that increased permeability of the obstructed loop led to transudation and transperitoneal absorption of toxin, but did not feel that venous absorption occurred, since the intestinal veins were ligated in their series of animals.

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The theory of vascular occlusion was supported by Dragstedt, Moorhead, and Burcky.[5] These investigators believed that toxins were normally present in the intestinal tract, but gained access to the blood only after the mucosa of the intestine had been damaged by vascular occlusion. Later experiments by these investigators, however, led to the belief that putrefactive processes were carried on by bacteria-produced lethal toxins, when absorbed through the lymphatics and general circulation.

Perversion of normal physiologic secretions of the intestinal mucosa has been adhered to by Stone, Bernheim, and Whipple.[6] These investigators found that animals with low ileal obstruction lived longer than those involving higher areas of the small intestine, especially the duodenum. They felt that the source of toxic material was the mucosa of the obstructed segment, produced not by bacteria, but by the secreting cells of the intestinal mucosa. The possibility of normal intestinal secretions becoming toxic upon absorption in high concentrations, or after undergoing a chemical change under the conditions of obstruction, is an intriguing one. Whipple[7] in 1911 believed that a primary proteose was the lethal factor in obstruction, but never demonstrated the presence of such a substance in the blood of experimental animals. Roberts[8] and Van Buren[9] believed that dehydration and chemical imbalance played a greater role in the cause of death than did the factor of toxicity.

Evidence for the occurrence of the preceding pathologic mechanisms is frequently seen in the clinical counterpart of the experimental closed loop. Estes and Holm[10] studied this type of lesion which was seen after side-tracking procedures done for adhesive obstruction. Such redundant segments of intestine produced distention, colicky pain, and ulcerative enterocolitis. Because of the possibility of such a complication, shunting operations for the relief of an obstruction should preclude the presence of a redundant loop.

Purpose and Scope.—The present study was undertaken to evaluate further the physiopathologic changes occurring in the closed loop type of obstruction. An attempt to learn more about the mechanisms culminating in the lethal end result of this lesion has been made. Special emphasis has been placed on the changes in serum proteolytic and antiproteolytic activity and the possible role played by them in relation to the fatal termination of the closed loop. The toxemia was studied from the aspect of both symptomatology and laboratory findings.

METHOD AND MATERIALS

A total of 26 healthy mongrels, each weighing 20 to 25 Kg., were operated upon. Food was withheld for 2 days prior to operation. Anesthesia consisted of sodium pentobarbital, 0.13 Gm. per kilogram of body weight, injected intravenously.

The abdomen was opened under aseptic technique and the duodenojejunal junction defined. A loop of jejunum, approximately 15 cm. in length and about 15 cm. distal to the ligament of Treitz, was selected. Kocher clamps were placed in the usual manner for an intestinal resection and the segment

of intestine was transected. The ends of the loop were then closed with a Parker-Kerr suture of 3-0 atraumatic catgut, followed by a running Lembert suture and a layer of 5-0 interrupted silk. The closed loop was returned to the peritoneal cavity with its blood supply intact. Continuity of the intestinal tract was re-established by an end-to-end anastomosis of the transected proximal and distal segments. The abdomen was closed with running 3-0 catgut suture for peritoneum, interrupted 3-0 silk for fascia, and 3-0 continuous silk for skin. Postoperatively, the animals were permitted fluids and mash as tolerated. No drugs or antibiotics were given during the postoperative period. An illustration of the closed loop appears in Fig. 1.

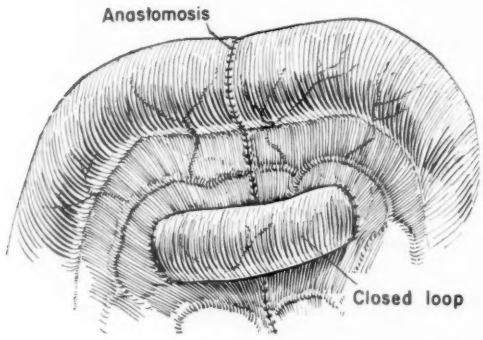


Fig. 1.—Experimental closed jejunal loop.

Laboratory studies were carried out before and every 2 days after establishment of the closed loop. These included determinations of serum proteolytic and antiproteolytic activity,[11] estimations of blood and plasma volumes, blood nonprotein-nitrogen and serum amylase determinations.

Bacteriologic and chemical examinations of the peritoneal and loop fluid were carried out following expiration. Chemical analysis included amylase and nonprotein-nitrogen determinations. Pathologic studies were made on sections of closed loop, kidney, liver, lungs, and loop mesentery.

RESULTS

Clinical Findings.—The clinical picture in experimental closed loop obstruction is that of a rapidly developing toxemia, occurring on the second or third postoperative day. This was manifested by an increase in heart rate, a temperature elevation to 104° F., and a decrease in peristalsis. Diarrhea and tarry stools were frequent symptoms and appeared in varying intensity. The toxic picture then either progressed in severity or gradually subsided. When toxemia became more severe, shock developed and death occurred suddenly from circulatory collapse. Animals recovering from the initial toxemia improved gradually over a period of 2 weeks. Those animals surviving longer than 2 weeks developed periods of remission and exacerbation of the toxemia.

Eleven animals exhibited perforations of the antimesenteric border of the loop; all died in 3 to 14 days. Fifteen had no perforations; of these, 9

died in 3 to 14 days. Of the remaining 6 animals, 3 expired in one month, 2 in 2 months, and the last was sacrificed at 9 months, the toxic picture having completely disappeared.

Pathologic Findings in Closed Loop Obstruction.—Autopsy revealed peritonitis with blood in the peritoneal cavity of most animals, varying in amounts from 25 to 500 c.c. The loops that had not perforated were tremendously distended and exhibited areas of necrosis along the antimesenteric border. Nonperforated loops contained about 100 c.c. of thick, black, digested blood, while those with perforations contained but little. Purulent inflammatory changes extensively involved both the mesentery and entire omentum.

Microscopic sections revealed hemorrhagic necrosis and infarction of the loop. There was autolysis of the intestinal wall involving the mucosa only, and ulceration of varying severity. The kidneys exhibited glomerular fibrosis and cloudy swelling of the tubules. The liver showed atrophy of the lobular cells, as well as separation of the liver cords. The lungs were atelectatic and exhibited marked hyperemia. The mesenteric veins and arteries were patent.

Laboratory Findings.—Smears of the peritoneal fluid showed gram-negative rods and gram-negative cocci, while cultures produced *Bacillus coli*, nonhemolytic streptococci, and *Clostridium welchii*. The loop fluid gave similar findings on both smears and culture. The results of chemical analyses on blood, peritoneal, and loop fluid appear in Table I.

TABLE I

LABORATORY FINDING	NORMAL VALUE*	TOXEMIA VALUE*
1. Blood volume	2.07 L.	0.79 L.
2. Plasma volume	1.31 L.	0.46 L.
3. Loop NPN	—	500.0 mg. %
4. Peritoneal fluid NPN	—	280.0 mg. %
5. Blood NPN	25.0 mg. %	50.0 mg. %
6. Loop amylase	—	1,295 Somogyi units
7. Peritoneal amylase	—	12,000 Somogyi units
8. Serum amylase	100 Somogyi units	2,400 Somogyi units
9. Serum proteolytic activity	25-35 mcg. tyrosine	125-150 mcg. tyrosine
10. Serum antiproteolytic activity	100 units	0-25 units

*Values appearing here represent the average values of 26 animals at the height of the toxemia.

Serum Proteolytic and Antiproteolytic Determination.—Proteolytic and antiproteolytic activity of the serum were determined by quantitating the acid-soluble tyrosine produced as the end product of digestion of a casein substrate. Suitable reagents were then added to the recovered protein-free filtrate and colorimetric technique applied. The density of the color developed was read on a Beckman DU spectrophotometer and the values converted to micrograms of tyrosine from a calibration curve which followed Beer's Law up to 300 mcg. concentration.

Proteolytic activity was measured in micrograms of tyrosine produced by the action of 0.1 ml. whole serum on the casein substrate. Antiproteolytic activity was defined as the amount of inhibitory effect of 0.1 ml. of serum on

tryptic digestion of casein. This was obtained by taking the difference in the amount of tyrosine produced by a standard trypsin solution acting on a casein substrate, and the tyrosine produced by tryptic digestion of casein in the presence of whole serum.

A. *Reagents:*

1. Sodium borate-sodium chloride buffer: pH adjusted to 8.0.
2. Casein substrate: a 5 per cent solution of casein in 10 per cent urea in a saline buffer.
3. Stock trypsin (Crystallin) in 0.05 normal hydrochloric acid, final concentration of 0.2 mg. trypsin per 1.0 ml.
4. Folin-Ciocalteau phenol reagent: 1 part added to 4 parts of distilled water.
5. Trichloracetic acid: 5 per cent solution in distilled water.
6. Sodium hydroxide: 2.5 normal solution prepared from 18 normal and titrated with 0.1 normal potassium acid phthalate.

B. *Procedure:*

1. Proteolytic enzymatic activity was determined by placing 0.1 ml. of serum and 0.1 ml. of 5 per cent casein in urea solution in a test tube. The volume was brought to 2.0 ml. distilled water and incubation was carried out at 50° C. for 4 hours. The undigested protein was precipitated by the addition of 3.0 ml. of 5 per cent trichloracetic acid, permitted to stand 30 minutes, and then filtered through a No. 50 Whatman filter paper.

The tyrosine content was then determined by placing 2.5 ml. of the protein-free filtrate obtained above, in a 25.0 ml. graduated test tube. This was followed by the addition of 2.5 ml. of distilled water, 2.0 ml. phenol reagent (1:4), and 1.0 ml. normal sodium hydroxide solution. The volume was brought to 10.0 ml. with distilled water and mixed. The color was permitted to develop for 40 minutes. The density was then read on the Beckman spectrophotometer and micrograms of tyrosine obtained by direct reading of the calibration curve.

2. Antiproteolytic activity was determined as follows: 0.1 ml. serum and 0.1 ml. casein substrate were placed in a test tube. To this was added 0.1 ml. standard trypsin solution (0.02 mg.). Similar amounts of trypsin and casein were placed in a second tube. The volumes in each tube were brought to 2.0 c.c. with distilled water and incubation was carried out at 50° C. for 4 hours. At the end of this period, enzymatic activity was halted and undigested protein precipitated by adding 3.0 ml. of 5 per cent trichloracetic acid to each tube. The chromogenic activity was then developed on 2.5 ml. protein free filtrate and the tyrosine content of each was determined by referring to the previously established calibration curve.

The antiproteolytic activity derived in micrograms of tyrosine produced following serum inhibition of tryptic digestion was expressed in units with

1 unit being equivalent to 10 mcg. of tyrosine. This might be designated by the following simple equation: where S = serum, C = casein, and T = trypsin: TC-STC = antiproteolytic activity.

C. *Results:*

Serum proteolytic and antiproteolytic activity values indicated the severity of the toxemia. Proteolytic activity became elevated from a normal preoperative value of 25 mcg. tyrosine, attaining values of 125 to 150 mcg. of tyrosine at the height of the toxemia. Antiproteolytic values fell from a normal of 100 units to 25 units. When the toxemia lessened, the proteolytic activity decreased and antiproteolytic activity exhibited a rise. However, when antiproteolytic activity fell to extremely low levels approaching zero, the prognosis inevitably was grave and all animals died in shock. These findings appear in Figs. 2 and 3.

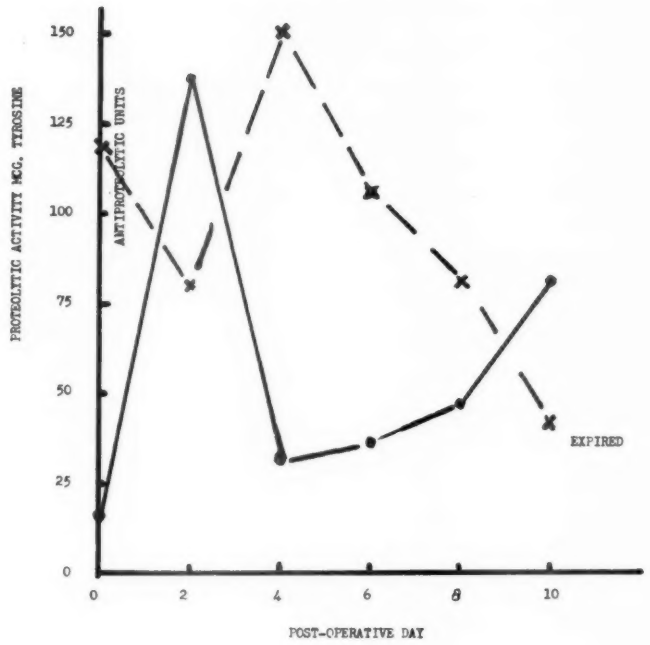
DISCUSSION

That closed loop obstruction presents a formidable problem in the disturbance of intestinal physiology was evident to us from the present experimental study. The fact that 60 per cent of the animals without perforated loops died as quickly as those with perforations attests to the profound toxemia that invariably develops in these animals. However, the fact that 6 animals lived for varying periods of time corroborates our feeling that compensatory mechanisms do exist, which attempt to alleviate the toxic changes that rapidly culminate in shock and death in the closed loop animal.

The depletion of blood and plasma volumes certainly hasten the onset of shock and vascular collapse, but are the result and not the cause of the underlying mechanism of toxemia. Certainly, Wangensteen[2] has given proof of the effects of increased intraluminal pressure on the impairment of venous drainage and increased permeability of the intestinal wall. Yet, in the present study, the mesenteric veins to the closed loop were entirely patent, so that venous drainage was presumably adequate up to a point substantiated by the absence of fluid in the peritoneal cavity in nonperforated cases. However, that venous return was in an unbalanced state was indicated by the tremendous dilated loops observed in several animals, who had survived the period of initial toxemia. At this point, permeability of the intestinal wall increased and blood seeped into the peritoneal cavity.

The role of bacterial production of toxins is certainly given credence by the works of Harper, Blaine, Nemir, and others[1, 4] and transperitoneal absorption can occur in the presence or absence of a patent venous system. The finding of large numbers of *Bacillus coli, Clostridium welchii,* and nonhemolytic streptococci in both loop and peritoneal fluid of this study is convincing evidence of their importance in the production of toxins. On the other hand, what was the mechanism that enabled 6 animals, in which the loops did not perforate, to overcome the initial period of toxemia and live for longer periods of time?

Fig. 2.



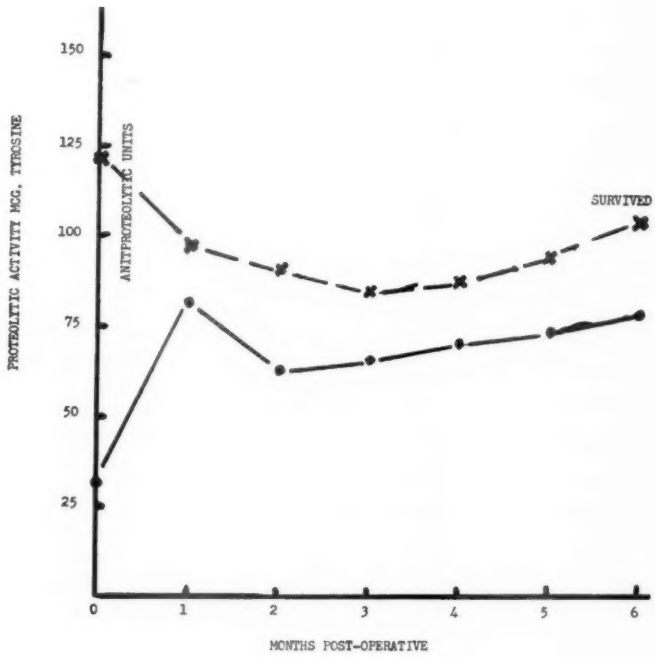


Fig. 3.

Figs. 2 and 3.—Serum proteolytic-antiproteolytic activity in closed loop intestinal obstruction. —— Proteolytic. — — — Antiproteolytic.

The concept of perversion of physiologic secretions of the intestinal mucosa, as advanced by Stone, Bernheim, and Whipple,[6] cannot be discounted. We believe that the toxins are proteolytic enzymes elaborated not only by bacteria, but from a mucosa damaged by bacterial autolysis. It is possible that neutralization of such enzymes by the antiproteolytic activity of the blood may permit a balance between excretion and absorption. With venous return adequate, proteolytic enzymes reaching the blood could be neutralized by the antiproteolytic systems and toxemia thus held in control. However, when mesenteric venous return no longer is able to balance the rate of excretion into the loop, the resulting dilatation and increasing permeability of the intestinal wall becomes apparent. Transudation and peritoneal absorption of proteolytic enzymes then occurs and rapid accumulation of these substances in the blood follows. The high concentration of toxic enzymes could then reduce antiproteolytic activity of the serum to such a level that profound anhydremia and death from vascular collapse would result. That this mechanism does take place appears to be evident to us from the changes in proteolytic and antiproteolytic activity that occurred in association with the clinical picture described earlier.

The specificity of the toxic enzymes is open to speculation. Globulin possesses proteolytic activity, but the reversal of A : G ratios observed in our experimental work probably resulted from hemoconcentration. The large increases in serum amylase, that were obtained during severe toxemia, might conceivably exert a toxic effect dependent upon their proteolytic structure. A third possibility might reside in the enzymes of *Clostridium welchii*. This organism produces two proteolytic enzymes, lecithinase and coagulase, both highly toxic in nature.

CONCLUSIONS

Toxemia produces the changes leading to vascular collapse, shock, and death in experimental closed loop obstruction. This syndrome appears to be initiated by an imbalance between secretions of both bacterial and intestinal proteolytic enzymes, and is dependent upon impairment of adequate venous return, vascular occlusion, and increased intraluminal pressure. The resulting increased permeability of the intestinal wall predisposes toward transudation and transperitoneal absorption of toxic enzymes. A deficit of antiproteolytic systems and their inability to inhibit proteolytic activity leads to shock and death. The control of toxemia in the clinical closed loop bcomes of paramount importance in relation to mortality rate. The use of antiproteolytic substances may possibly improve a poor surgical risk and thus more safely permit surgical intervention.

SUMMARY

Experimental closed loop intestinal obstruction has been produced in 26 dogs, the clinical course described, and the pathologic mechanisms discussed.

Emphasis has been placed upon the importance of proteolytic and antiproteolytic systems and their role among the factors leading to the fatal termination in this type of obstruction. The use of antiproteolytic substances in the patient with closed loop obstruction might reduce the risk of surgery.

Appreciation is expressed to Mrs. Gloria Hetrich for performing the required chemical analyses.

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THE EFFECT OF ECK AND REVERSE ECK FISTULA IN DOGS WITH EXPERIMENTAL DIABETES MELLITUS

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SINCE the time of Eck, investigators have been intrigued by the physiologic changes induced by portacaval shunt, in which the liver is partially devascularized by diversion of the splanchnic drainage directly into the systemic venous system. It is now clear that portal-systemic venous shunts are attended by changes in protein metabolism which are of considerable clinical importance.[8] Knowledge of the changes in carbohydrate and fat metabolism is less well developed.

The present study was undertaken to determine if experimental diabetes in dogs was altered by the formation of a portacaval shunt. Conversely, to determine if augmentation of hepatic blood flow resulted in any change in the diabetic state, a companion study of the influence of reverse portacaval shunt on experimental diabetes has been included.

METHODS

Healthy mongrel dogs weighing from 10 to 18 kilograms were kept in metabolism cages and quantitative 24-hour urine specimens were collected at 8 A.M. The animals were fed daily at 4 P.M. The quantity of meal was constant and contained 24 per cent protein, 7 per cent fat, and 67 per cent carbohydrate, and fiber with vitamin B, C, and D supplement. Dogs with diabetes received commercial protamine zinc insulin at 9 A.M. daily. The dose was regulated by the previous day's quantitative glucose excretion.

Alloxan diabetes was produced by the method of Goldner and Gomori.[3] Eck fistula was formed by the technique of Freeman.[1] Reverse Eck fistula was produced by side-to-side portacaval anastomosis with ligation of the vena cava above the entrance of the adrenal veins.[9]

Reducing substance in the urine was measured with Benedict's quantitative solution. Blood samples were treated with sodium fluoride and glucose measured, using a Somogyi filtrate, by colorimetric determination on the autoanalyzer. The method of colorimetry was based on the reduction of potassium ferricyanide in the presence of potassium cyanide.

THE EFFECT OF ECK FISTULA ON 5 DOGS WITH ALLOXAN DIABETES

Insulin Requirement.—After the injection of alloxan and the appearance of glycosuria, 4 to 8 weeks elapsed during which the daily insulin requirement

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was determined. When the animals appeared to be in a stable metabolic state, portacaval shunt was performed.

A typical experimental animal is shown in Fig. 1. Immediately after operation, the necessary insulin dose was not appreciably altered. One week after surgery, a marked increase in insulin requirement became manifest. This occurred in all dogs from 1 to 5 weeks postoperatively. After this phenomenon was first observed in a given dog, the insulin requirement progressively rose (Fig. 1) until the dog was either sacrificed or died. The ultimate daily insulin dosages were 3.3, 3.0, 2.8, 2.0, and 1.5 times higher than had been required prior to operation. The average daily insulin injection preoperatively was 16.4 units and postoperatively the ultimate requirement averaged 44 units.

The Effect of Fasting on Blood Sugar and Glycosuria.—Two diabetic dogs with Eck fistula were subjected to periods of starvation. Food deprivation resulted in an abrupt diminution or cessation of glycosuria (Fig. 2). During a period of fasting (as long as 3 days) blood sugar fell toward normal values (Fig. 2). As soon as the diet was resumed the diabetic state quickly reverted to the pre-existing condition with glycosuria and elevated blood sugar.

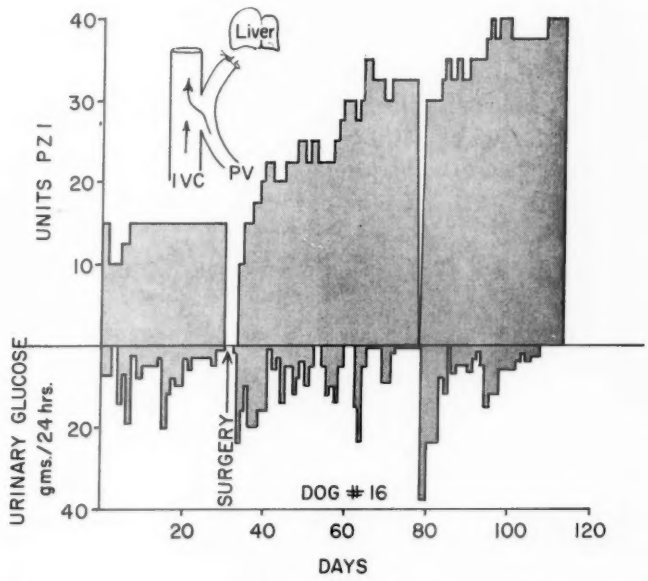

Fig. 1.—Daily insulin requirement in a dog with alloxan diabetes before and after Eck fistula. Included is data on 24-hour urine sugar excretion. Note the sharp rise in insulin requirement after surgery.

THE EFFECT OF REVERSE ECK FISTULA ON 2 DOGS WITH ALLOXAN DIABETES

Insulin Requirement.—Two dogs with stable alloxan diabetes were subjected to simple reverse Eck fistula. Insulin requirement in these animals was slightly increased but the excessive alteration noted in diabetic Eck fistula dogs was not seen. The course of the diabetes in this preparation is shown in Fig. 3. The ultimate daily insulin dosages were 1.3 and 1.1 times higher than had been present prior to operation. The average daily preoperative insulin

requirement was 21 units and the ultimate postoperative requirement averaged 25 units. No difference was noted in effect during test periods during which all injections were given either in the foreleg or hindleg.

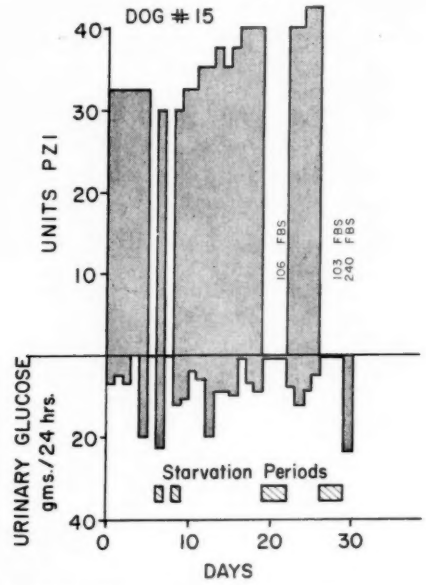

Fig. 2.—Influence of starvation on glycosuria and blood sugar in a dog with alloxan diabetes and Eck fistula. With food deprivation, glycosuria ceases and blood sugar elevation is minimal or absent.

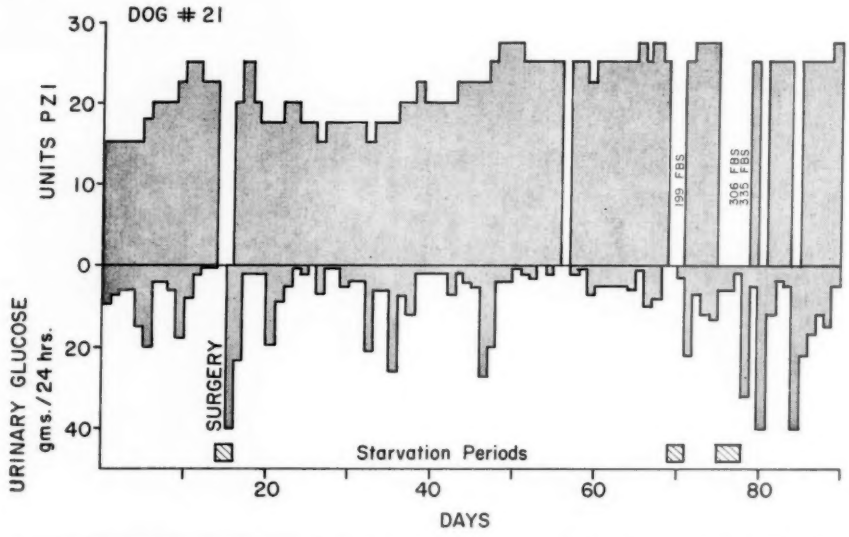

Fig. 3.—Daily insulin requirement in a dog with alloxan diabetes before and after reverse Eck fistula. Also shown is the effect of starvation on glycosuria and fasting blood sugar.

The Effect of Fasting on Blood Sugar and Glycosuria.—Food deprivation in these animals caused a distinctly different effect than in the diabetic dogs with Eck fistula. Despite starvation, glycosuria continued in both animals and blood sugars remained elevated (Fig. 3).

Clinical Behavior.—The animals were healthy and presented no maintenance problems except for the care of the diabetes.

COMPARISON OF CLINICAL BEHAVIOR OF DOGS WITH ECK FISTULA ALONE, AND DOGS WITH DIABETES PLUS ECK FISTULA

Eck Fistula Alone.—A control group of 4 normal dogs were subjected to Eck fistula. After operation, these animals were all unhealthy. They all had weight loss, episodic stupor, and convulsions characteristic of meat intoxication. These animals all died within the first 5 postoperative weeks.

Eck Fistula Plus Diabetes.—The clinical behavior of the 5 dogs with Eck fistula plus diabetes provides an interesting contrast to the nondiabetic dogs with Eck fistula. Their health was much better. Only one animal had weight loss, and 2 gained weight postoperatively. Two animals died in the night during the third postoperative month (probably from insulin reaction) and the remaining 3 were sacrificed in good health during the second, third, and fourth months after surgery. None of the animals manifested the episodic stupor, staggers, or blindness which were noted in the dogs with Eck fistula alone.

AUTOPSY FINDINGS

Gross examination of all dogs operated upon was conducted. In each case, the anastomosis was patent. The dogs with Eck fistula had livers which were smaller than normal. There were no consistent gross abnormalities of the pancreas.

DISCUSSION

The influence of Eck fistula on experimental diabetes has been the subject of previous investigation with apparently contradictory results. After pancreatectomy, Hendrix and Sweet[4] described alleviation of the diabetes following Eck fistula, under conditions of prolonged fasting. Similarly, Mann and Magath[7] found that fasting hyperglycemia did not develop with the combination of pancreatectomy, Eck fistula, and partial hepatectomy. In contrast, Koide and Freeman[5] found alloxan diabetes to be chronically aggravated in 4 of 5 dogs receiving regular feedings. The present data suggest that these seemingly discrepant observations are due to the fact that, in some of the previous investigations, the dogs were being fed, and that, in others, the animals were being starved. In the present study it was shown that dogs with diabetes plus Eck fistula are unusually sensitive to alterations in carbohydrate intake. When on a standard laboratory diet the amount of insulin necessary to control glycosuria is considerably increased. When food is withheld, glycosuria rapidly disappears, blood sugars fall toward normal, and insulin is no longer required.

That the liver has an important role in the hemostatic control of blood sugar level has been known for some time.[6, 11, 12] It seems reasonable to believe that the progression in alloxan diabetes observed after the construction of an Eck fistula is related in some way to the deviation of portal blood flow away from the hepatic bed, but the mechanism of this effect is not clear. Presumably, it could result from the suppression of liver function known to follow Eck fistula,[2, 10] as suggested by Koide and Freeman.[5] A second aggravating factor could be the absence of primary passage of alimentary glucose through the hepatic bed, a circumstance which would remove oral glucose intake from im-

mediate regulatory control by the liver. An additional unexplored possibility is that there is an alteration in insulin metabolism following Eck fistula.

The protection apparently afforded Eck fistula dogs by the addition of diabetes will require further study. Conceivably it is related to the hyperglycemia present with diabetes. Any explanation of this effect would be conjectural but it seems likely that some abnormality of protein metabolism associated with the meat intoxication of Eck fistula is alleviated by changes in the metabolic pattern present with diabetes.

SUMMARY

1. Dogs with alloxan diabetes were subjected to Eck fistula. This procedure produced a marked increase in the amount of insulin necessary to control glycosuria. When the dogs were fasted, glycosuria disappeared, blood sugars fell toward normal, and the need for insulin was eliminated.

2. Reverse Eck fistula was created in dogs with alloxan diabetes, and resulted in minor increases of doubtful significance in daily insulin requirement. When fasted, the blood sugar of these animals remained elevated and glycosuria continued.

3. Nondiabetic dogs with Eck fistula all died of meat intoxication. Dogs with Eck fistula plus diabetes had no evidence of meat intoxication and in general were in better health than dogs with Eck fistula alone.

4. Possible mechanisms of the role of Eck fistula in the alteration of the diabetic state are discussed.

It is a pleasure to acknowledge the encouragement and guidance of Drs. John J. Farrell and A. G. Hills. The work would not have been possible without the unselfish cooperation of Mrs. Anna Louise Rundell in the performance of the chemical analyses, and Barbara Starzl in the assistance of technical procedures.

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A BIOCHEMICAL DISSECTION OF ISCHEMIC LIVER NECROSIS

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INTRODUCTION

THE general plan of this study is to review some of the pertinent work of surgeons and biochemists and to present additional work from this laboratory in an effort to define some of the more obvious biochemical changes of a dying organ. The recent flood of literature on the diagnostic use of serum glutamic oxalacetic transaminase (SGOT), in situations in which cell damage is known to occur, suggested its use in seeking a better understanding of the early critical period in liver cell damage after interruption of blood flow. SGOT is a soluble intracellular protein located primarily in the cytoplasm and the pattern of its release might be expected to define the period of early cell disruption which leads to irreversible changes.

Depriving organs of their blood supply will inevitably change the structure of the tissue and, depending on the degree of damage, lead to death of the organ. However, morphologic changes may not be recognizable for 4 to 6 hours.[18] The nucleus will then show chromatin precipitates, mitochrondia will show swelling, and cytoplasmic protein will show precipitates and vacuolization. The early changes and the sequence of these changes must be studied by biochemical methods.

Interference with energy metabolism is a prime factor in cell deterioration.[17] Although endogenous substrate, such as glucose, can supply some energy anaerobically, the store of this substrate soon becomes depleted. The catabolic process of glycolysis and the inhibition of the Krebs cycle will result in the accumulation of anions.[26] There is a net increase in the ionic strength of the protoplasm; consequently, water moves into the cell. There is swelling of the whole cell[34, 37] and also of the mitochondria.[8] Cell membrane transport is normally an active metabolic process but any breakdown of energy supply will allow purely physical properties of the cell wall to come to the fore. Thus, Mg^{++}[40] and K^{+} leave the cell and Na^{+}[37] and Ca^{++}[33] enter. The swollen mitochondria are unable to exhibit any oxidative phosphorylative function due to the secondary depletion in respiratory co-factors.[15] Diphosphopyridine nucleotide (DPN) and adenosine triphosphate (ATP) decrease and inorganic

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phosphate accumulates.[6, 26, 41] The hydrogen ion concentration increases and, when the pH approaches 6, cathepsins are activated[2] and proteolysis proceeds to the final destruction and lysis of cell protoplasm.[18]

In many reports, death of the animal had been the end point in investigations of the liver susceptibility to interruption of blood flow.[13, 19] This tells something about the susceptibility of the animal under the stated experimental conditions but may not indicate accurately the susceptibility of the liver as an organ, or of liver cells, to deprivation of blood flow. The early works on autolysis were concerned primarily with postmortem proteolytic breakdown of liver which continues over a period of days. It was extensively reviewed by Bradley[3] in 1938. Some of the changes could be accounted for by an anaerobic spore-bearing bacterium present even in healthy dog liver.[44] Hepatic artery ligation, which proved fatal in control animals, was tolerated by animals treated with penicillin.[27] Penicillin also protected animals from fatal peritonitis secondary to implanted dog liver.[24] Probably collateral hepatic artery blood flow accounts for survival of dogs after hepatic artery ligation.[14] Where interruption of arterial flow has been proved by injection and x-ray techniques, necrosis and death results.[16, 26] Clinically and experimentally clamping both hepatic artery and portal vein for more than 30 minutes is fatal, despite antibiotics.[31] Clamping the aorta for 60 minutes above the superior mesenteric artery was tolerated without fatality in dogs, but for only 20 minutes above the celiac axis.[4] The difference was thought to be due to the susceptibility of the liver. It was then observed that dogs with portacaval shunts could recover from a 75-minute clamping of structures at the liver hilum, whereas a 90-minute interruption was fatal.[12] Complete ligation of hilar blood vessels going into the liver in dogs with portacaval shunts did not cause death before an average of 33 hours, which is about as long as the hepatectomized dog will survive.[12] Variability in death rate with these different types of experiments illustrates the fallacy of using death of the animal as an index of the susceptibility of the liver cells to interruption of blood flow.

Marked suppression of aerobic metabolism in liver slices occurred after even 15 minutes of blood flow interruption, but recovery was rapid.[43] Longer periods of interruption caused greater suppression and slower recovery. A 2-hour period of blood flow interruption resulted in sufficient damage so that very little recovery occurred. Others have reported on the fall in blood pH[1] and a loss of potassium[38] following temporary interference with blood flow. These are important observations, but they do not tell much about the integrity of the cell.

In this study, we found that SGOT was not released under certain conditions in which cell damage should be present, and in such experiments we investigated beta-glucuronidase release. This enzyme is part of a group of hydrolytic enzymes present in mitochondrial particles, which have been termed "lysosomes" by DeDuve and his associates.[11] The lysosomes contain ribonuclease, desoxyribonuclease, cathepsin, and acid phosphatase. When these lysosomes are incubated at 37° C. and at pH 5, they begin to release their hydrolytic enzymes which reach 75 per cent of full activity in 30 minutes. Although

DeDuve and his co-workers observed this in vitro, one might assume similar conditions to occur in the damaged cell. The release of beta-glucuronidase gave an index of change in those mitochondria called lysosomes, which is an early cytoplasmic change, and may be a direct measure of one of the factors responsible for autolysis.

METHODS

Clamping the Hepatic Blood Supply.—Healthy dogs were anesthetized with 25 mg. pentobarbital sodium per kilogram of body weight. The abdomen was opened with a midline incision under sterile conditions. The hepatic artery and portal vein were dissected free and the respective vessels were clamped for a specified period of time. After removal of the clamp, the abdomen was closed. Heparinized venous blood samples were drawn before surgery and at known time intervals after clamping for SGOT analysis. After the operative procedure, penicillin and streptomycin were given to the dogs in the first part of the series, but as antibiotics did not appear to affect the early change under study, their use was discontinued.

Injections of SGOT to Determine the SGOT Space.—Healthy dogs were infused with known volumes of plasma containing approximately 250 units of SGOT per milliliter. This plasma was prepared in the following manner. The portal triad was clamped for 30 minutes as described. Two hours after release of the clamp, the donor dog was heparinized and exsanguinated and the plasma separated. After a control sample was drawn from the recipient dog, the high SGOT plasma was injected into a vein, and the SGOT level in the venous blood was followed for one day.

Perfusions of Isolated Livers With Nonaerated Blood.—Healthy dogs weighing 15 to 30 Kg. were anesthetized with 25 mg. of Nembutal per kilogram of body weight. Heparin, 1.5 mg. per kilogram of body weight, was injected and a control blood sample was drawn. The dog was bled through the femoral artery. An appropriate volume of this blood was added to an equal volume of 0.155 M phosphate buffer, pH 7.4, and used as perfusate. The hepatic veins were drained by cannulae inserted through the vena cava which was ligated above and below the liver. A negative venous pressure was maintained to obviate loss of blood. The perfusate was kept at 37°, 34°, or 26° C. by the use of a constant temperature water bath. The perfusate was pumped from the reservoir by a Sigmamotor pump into the portal vein. A mean blood pressure of 10 mm./Hg was maintained throughout the perfusion. Blood flow at the rate of 300 ml. per minute was established within 20 minutes of exsanguination. Samples from the perfusate were taken at regular time intervals. In later experiments, it was found more convenient to remove the liver from the dog and place it in the perfusate. The perfusate was then pumped into the portal vein and ran out from the open hepatic vein. The results of all perfusions were corrected for perfusate loss from sampling and to a standard dog weight of 15 Kg. and a standard perfusate volume of 1,000 ml.

Chemical Methods.—SGOT was determined according to the Steinberg, Baldwin, and Ostrow's[36] modification of Karmen's method.[20] Kerr and Levvy's[21]

modification of Talalay, Fishman, and Huggins method[39] was used for determining beta-glucuronidase. Glutamic pyruvic transaminase (GPT) was measured by the method given by Wroblewski and La Due.[45] Sodium and potassium were determined using the Baird flame photometer. Magnesium was determined by the colorimetric method of Orange and Rhein.[30] The Cambridge pH meter was used for determining pH, with an accuracy of 0.01 pH units. The chemicals used in the estimation of SGOT and GPT as well as the substrate for beta-glucuronidase (cinchonidine derivative of phenolphthalein glucuronide) were purchased from the California Biochemical Corporation. The cinchonidine derivative was converted into the free sodium salt of phenolphthalein glucuronic acid in our laboratory according to the method of Colowick and Kaplan.[7] All other chemicals used were analytical grade laboratory reagents.

RESULTS

Portal Triad Clamping.—Raffucci and Wangensteen[32] have reported that 15-minute clampings are generally safe but above this time the mortality rate increases rapidly. These authors reported 25 per cent mortality after 25 minutes, 75 per cent after 30 minutes, and 100 per cent after 45 minutes of clamping. We found that interruption of 25 minutes or less did not result in death of the animal, but did result in liver damage, as measured by the release of SGOT.

The portal triad was clamped in 16 dogs for periods between 5 and 25 minutes. None of these dogs died following the experiment. After removal of the clamp, the SGOT level in the blood was followed until it reached the control level. Typical results are shown in Fig. 1. Immediately after release of the clamp, the SGOT level rose sharply and reached a peak. After clamping of more than 15 minutes, the time to reach the peak varied independently of the clamping time and ranged from 60 minutes to 500 minutes, averaging 215 minutes. Sham operated animals used as controls showed no elevation of SGOT in the blood. Clampings of less than 15 minutes did not result in enough damage to double the dog's base level. However, some enzyme was released no matter how short the clamping period. When the clamping period was 15 minutes or more, the SGOT level was doubled or more in all cases. The curves corresponding to the short clamping periods (up to and including 15 minutes) show an immediate fall of the SGOT level after the peak was reached, whereas there was usually a continuous high level of SGOT when the clamping period exceeded 15 minutes. In 4 dogs in which the portal triad was clamped for 12 to 25 minutes, a bimodal SGOT curve was seen corresponding to Curve *D* in Fig. 1. The second rise might be due to intravascular clotting in the liver or alteration of circulation from other causes which temporarily prevents released enzyme from some areas of liver from reaching the general circulation.[9, 10]

A SGOT release curve for each of the 16 triad clamp experiments was plotted on a linear scale and integrated for an estimate of total enzyme release by measuring the area under the curve with a planimeter. This method is not exact, as the area is a function of the plasma clearance rate of the enzyme as well as release of enzyme from the liver. However, it should

theoretically give a closer approximation for comparison of total SGOT released than merely comparing peak values. The log of the areas (y) was then plotted against clamping time (x). The line of least square fit was calculated and follows the equation: $y = -1.11 + 0.18\ x$. The standard deviation of y was 0.633 and the correlation coefficient was 0.7510. This is given to present a large volume of data and demonstrates the wide variability of enzyme release among dogs under the conditions described. It indicates that the total amount of enzyme released, following temporary blood flow interruption, bears an exponential relationship to the duration of that blood flow interruption.

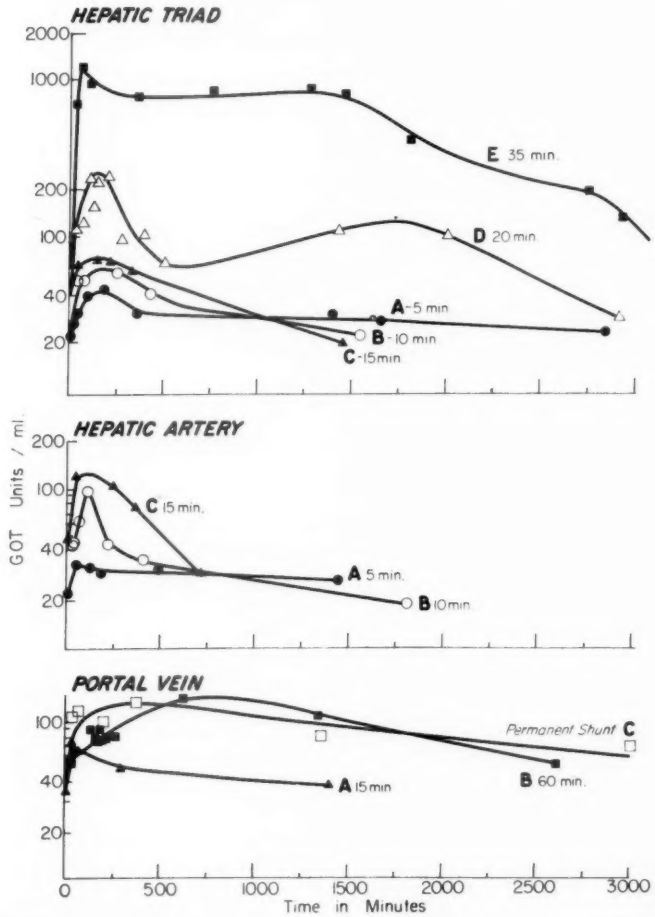

Fig. 1.—Typical experiments are shown in which the hepatic triad, hepatic artery alone, and portal vein alone were clamped. For graphing convenience, a semilog plot was used. The clamp was applied at zero time and left for the time indicated. The portal vein experiment B is an exception in that two 30-minute clampings were used with an interval of 90 minutes. Portal vein C represents an experiment in which the portal flow to the liver was permanently interrupted at zero time.

In seven of the portal triad clamping experiments and several injection experiments GPT was also determined. Because of its slower rise and slower clearance, it was not as useful an index of the immediate damage as SGOT, but the findings served as an additional index of degree of injury which was confirmatory.

2. *Hepatic Artery Clamping.*—The hepatic arterial inflow at the liver hilum was clamped for periods of 5, 10, 15, and 30 minutes in 8 experiments using 4 dogs. Typical curves are shown in Fig. 1. Enzyme release after 5, 10, and 15 minutes clamping of the hepatic artery is comparable to the similar periods of portal triad clamping.

3. *Portal Vein Clamping.*—Fig. 1 shows the response of dogs in SGOT release to clampings of the portal vein. In the animal in which the period of portal vein clamping was 15 minutes, the level of SGOT release was less than most hepatic artery or portal triad clampings for the same period of time. Another dog was subjected to two 30-minute clamping periods separated by 90 minutes. As may be seen, the maximum response was an elevation of enzyme to only 130 units.

Two dogs were prepared with end-to-side portacaval shunts. These dogs had SGOT levels of 45 and 114 units per milliliter 2 weeks after the procedure, indicating continued minor liver damage. The portal vein was then clamped for 15 minutes, unclamped for 90 minutes, and clamped again for 15 minutes in one dog. The same procedure, but with 30-minute clamping periods, was used in the second dog. Neither dog had any further elevation of enzyme after these interruptions. These experiments constitute a necessary control for the other clamping experiments and indicate that the increase of SGOT observed was due to liver and not intestinal damage.

The clamping experiments cannot be very well-controlled experiments. After interrupting blood flow for a given length of time through the liver, the release of the clamp does not lead to restoration of normal circulation. In order to have the animal recover, one cannot cut off the liver's blood supply for more than 30 minutes. Even in a 25-minute clamping experiment, there is pooling of blood in the portal bed with a progressive fall in blood pressure and, by 30 minutes, the mean arterial pressure is less than 30 mm. Hg. Recovery of pressure takes about 40 minutes. Even when blood flow is restored, liver circulation may not be normal. These uncontrollable variables suggested the need for experiments in which blood flow is maintained at a constant level. An attempt was made to overcome some of the mentioned deficiencies by using liver perfusion experiments.

*Liver Perfusions With Nonaerated Blood.**—The results of 10 perfusion experiments, carried out with nonaerated blood at 38°, 34°, and 26° C. are represented in Fig. 2. SGOT was released sooner at high than at low temperatures. Thus, at 38° C., the enzyme appeared after approximately 70 minutes.

* In order to use a volume of perfusate which would be comparable to a normal animal, the SGOT space was determined. The following type of experiment was carried out in order to get an approximation of the SGOT space: Plasma with high SGOT levels, obtained from donor dogs as described in the section of Methods, was injected into 4 dogs. The SGOT in the blood was followed until it fell to the base level. Enzyme level was plotted as a function of time on a semilog scale and the resultant straight line extrapolated back to zero time. This provided the initial concentration of SGOT (C_2). The effective SGOT space was then calculated from the following relationship:

$$\text{SGOT space in ml./Kg.} = \frac{(V_1)\ (C_1)}{C_2} \cdot \frac{1}{\text{Dog wt. in Kg.}}$$

V_1 is milliliters of plasma injected, C_1 is units of SGOT in 1 ml. of plasma, and C_2 is units of SGOT in 1 ml. of blood at zero time as determined by the observed disappearance curve. The average SGOT space, as determined in 7 experiments, was found to be 67 ml. per kilogram of dog weight. With this value and the total weight of the dog, whose liver was to be used, the volume of perfusate was calculated.

At 34° C., the time interval was approximately 100 minutes, and, at 26° C., the enzyme was not released until 135 minutes. Increasing the temperature resulted also in a greater total release of SGOT. Again, as had been found in clamping experiments, there was considerable variation between dogs.

In one typical experiment of each temperature group, magnesium and beta-glucuronidase were determined in addition to SGOT. The findings are represented in Fig. 3. The results of the 34° C. experiment, which fell in between the high and the low temperature group, were left out for graphical clarity. In all three experiments, magnesium and beta-glucuronidase release was apparent within 25 minutes, which was significantly before the SGOT release. Their rates of release remained constant over the whole perfusion period and were temperature dependent.

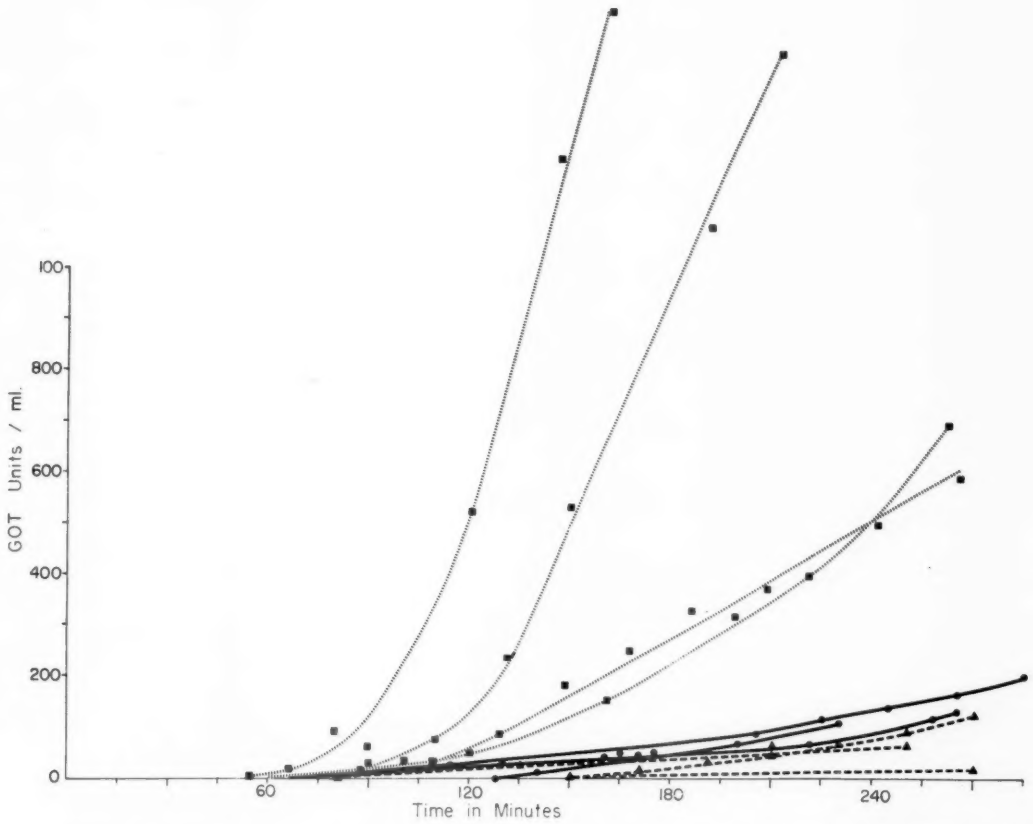

Fig. 2.—Ten liver perfusion experiments are shown: ■·····■, 38° C.; ●——●, 34° C.; and ▲------▲, 26° C. The concentration of SGOT in the perfusate is plotted against time, using the time of exsanguination of the dog as zero time. The data from each experiment were standardized to a zero base line SGOT level.

Fig. 4 shows the results of a liver perfusion at 34° C., in which the nonaerated perfusate used was one part blood plus one part plasma. It can be seen that the sodium fell and the potassium rose in equivalent amounts and reached an equilibrium at approximately 170 minutes. SGOT did not rise appreciably until after this equilibrium had been established. An immediate respiratory acidosis occurred. The pH of the perfusate then decreased slowly

from 7.16 to 7.05 in the first 200 minutes, and fell to 6.7 within the next 100 minutes while SGOT was released at an increasing rate. Magnesium rose continuously throughout the perfusion.

In one of the perfusion studies, the osmotic pressure was measured in the perfusate by freezing-point depression and was found to increase at a steady rate. A continuous loss of dry weight of the perfused liver was found. Other workers, while studying the effect of hemorrhagic shock in rat liver, reported a decrease of dry weight of one-third to one-half and interpreted this as an expression of disorganization and loss of integrity of liver tissue.[35]

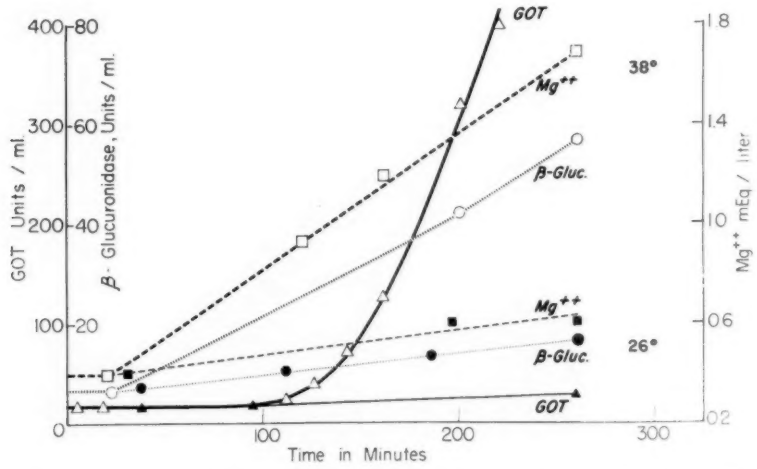

Fig. 3.—The release of SGOT, beta-glucuronidase, and Mg is shown in 2 dog liver perfusion experiments carried out at 38° C. (△, ○, □) and 26° C. (▲, ●, ■).

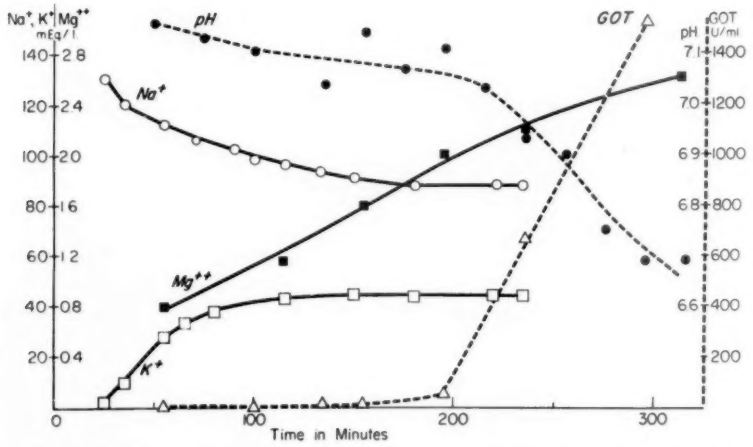

Fig. 4.—A liver perfusion experiment carried out at 34° C., with blood and plasma as perfusate, shows the early diffusion of Na^+ and K^+, the late release of SGOT and H^+, and the slow steady release of Mg^{++} and summarizes, in one experiment, some of the sequential relationships observed in the release of each moiety.

DISCUSSION

In the early stages of the perfusion experiments, SGOT release did not occur and therefore tells less about cell changes during this critical period than the measurement of beta-glucuronidase and magnesium. SGOT is in the soluble

fraction of the cell whereas beta-glucuronidase and magnesium are associated with mitochondria. Release of beta-glucuronidase from the cell must involve loss of integrity of the lysosome particles, which are types of mitochondria, and diffusion of this enzyme across the cell membrane. In view of the destructive nature of the hydrolytic lysosomal enzymes this early release of beta-glucuronidase carries implications far greater than the release of other cellular material. Beta-glucuronidase appeared in the perfusate at a time when SGOT could not pass the cell membrane. Little is known about the relative size, configuration, isoelectric point, and other factors, including cell membrane alterations, which might influence the diffusability of these two enzymes. It may also be that lysosome particles are among the more susceptible organelles. This observation might serve as a warning that there may be circumstances in which failure of SGOT release does not necessarily indicate a healthy state of affairs within the cell. On the other hand, the release of SGOT certainly suggests a profound alteration in structure and function of the cell. In the clamping experiments, some SGOT was released no matter how short the clamping period. Thus, even brief interference with blood flow proved to be noxious. This is consistent with the hypothesis that the volume of viable liver tissue is a function of blood flow volume, a hypothesis supported also by liver regeneration experiments.[5]

It is surprising that after interruption of blood flow, the reintroduction of arterial blood causes release of cellular enzymes. While in perfusion experiments with nonoxygenated blood, no SGOT was released for 90 minutes, the release of SGOT in clamping experiments, after reinstitution of normal oxygenated blood flow, was almost immediate. This apparent aggravation of damage to tissues, by re-establishment of arterial circulation, has been observed previously by several workers studying morphologic changes in liver and kidneys.[22, 28, 29]

The striking difference observed in the pattern of SGOT release between the clamping and perfusion experiments involves a more profound study of the intracellular changes. A possible explanation can be found in a recent article by Lehninger and his co-workers[23] who state, "The molecular and geometrical configuration of the mitochondrial membrane is a function of the oxidation-reduction state of the respiratory carriers; recent experiments have demonstrated that when the electron carriers of intact mitochondria are fully reduced, the mitochondria are not as susceptible to swelling in the presence of thyroxine and other agents. When the carriers are fully oxidized, the mitochondria are maximally responsive to the action of swelling agents."

The changes which accompany the cessation of aerobic metabolism and institution of anaerobic glycolysis probably set the stage for mitochondrial and cell membrane swelling and subsequent mechanical disruption. In the case of lysosomal particles, early dissolution does occur. Lysosomal enzymes are therefore anaerobic, not only in activity but in release and activation. At the same time, the reduced state may defer or diminish the actual swelling and disruption of the cell membrane and other components of cell structure. Even in the absence of oxygen, as seen in the perfusion experiments, the cell eventually breaks down and SGOT is released. It has been demonstrated that, under anaerobic conditions, substrate is the limiting factor in preserving the oxidative

phosphorlyating system during the initial 30 minutes.[15] Thus, in our experiments, variation in the level of glucose in the perfusate and variation in the intracellular stores of glycogen must be considered.[46] Some protection against damage might be demonstrable by building up these stores. An apparent beneficial effect of feeding, prior to liver anoxia, has been observed.[42]

The perfusion experiments permit a study of the effect of temperature on cell breakdown. That tissue damage may be prevented or delayed by cooling is well established. Cooling the perfused liver from 38° to 34° C. had almost as great an effect in delaying SGOT release as cooling to 26° C. In view of the deleterious effects of extreme hypothermia on cardiac rhythm, it would appear that only mild cooling might provide maximum benefit with minimum risk.

Controllable variables and combinations of variables need further study in the search for minimal damage with a maximum period of blood flow interruption. Immediate application of such findings may not be possible but the problems involved are pertinent to treatment of liver tumors, portal hypertension, shock, and, in fact, any condition wherein there is temporary or permanent decrease in liver blood flow.

SUMMARY

1. In dogs, the hepatic triad, the portal vein, and the hepatic artery were clamped for varying periods of time and the release of serum glutamic oxalacetic transaminase (SGOT) was studied.

2. Even a 5-minute interruption of the portal vein or hepatic artery blood flow resulted in a definite increase in SGOT release. Total enzyme release was exponentially proportional to duration of occlusion of the vessels.

3. Isolated dog livers were perfused with nonaerated blood under various conditions. In all cases, no SGOT was released for a period of at least 90 minutes. This period was even longer when the temperature was lowered from 38° to 34° or 26° C. This finding was discussed and compared with the immediate release of SGOT in the clamping experiments after re-establishment of blood flow.

4. The early period of no SGOT release in perfusion of liver with nonaerated perfusates was investigated further. It was found that Na^+ and K^+ diffused across the cell membrane in equal amounts and reached an equilibrium at about the time when the pH fell below 7.0 and when release of SGOT began. Furthermore, beta-glucuronidase and Mg^{++} appeared in the perfusate immediately and rose linearly with time. The significance of the two enzymes in terms of autolytic sequence is discussed and special attention is given to the potential role of lysosomes.

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DESMOID TUMOR OF THE ABDOMINAL WALL: USE OF PREDNISONE TO PREVENT RECURRENCE IN A CHILD

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DESMOID tumor of the abdominal wall is uncommonly encountered in adults and very rarely seen in children. In a recent survey of tumors of infancy and childhood studied over a 15-year period at a major medical center, no such lesion was discovered among 768 benign tumors, although 5 fibromas of the hand were observed.[1] Booher and Pack[3] summarized the reported literature and found 20 cases from 1893 to 1951, including 3 of their own. The tumor is a benign, unencapsulated, fibrous neoplasm which may grow to a large size and/or cause extensive local infiltration and destruction of adjacent striated muscles; it may become fixed to surrounding structures, such as bone.[2] Because of these characteristics, wide excision has become the operation of choice. The danger of recurrence is great and ensues rapidly after incomplete removal. Subsequent removal may be difficult or impossible and may require drastic general and plastic surgical assault.[4] Recurrence appears to be more likely in children than in adults,[2] and at least one death has been reported as a result of repeated recurrences with complications of exuberant infiltration (intestinal obstruction with peritonitis[3]).

This presentation reports the apparently successful use of a glucocorticoid hormone (prednisone) in the dissolution of a recurrence of desmoid tumor of the abdominal wall and suppression of subsequent recurrence over a 3-year period. The patient had undergone 2 operations for extensive resection of the widely infiltrating desmoma and upon the reappearance of tumor following the second operation, administration of the hormone was instituted.

CASE REPORT

K. A. B., a white girl, was first admitted to The University of Texas Hospitals on July 6, 1954, at the age of 22 months with the chief complaint of "bladder tumor." Three days prior to that date, the mother had noted a firm, nontender mass in the lower mid-abdomen. The child had no complaints. There was a history of a fall from a bicycle in which the abdomen had been struck on the handle-bar, some weeks earlier. In May, 1954, the patient had been discovered to have bilateral pyelectasis, and plastic repair of the right ureteropelvic junction and pyelostomy were carried out. Both the mother and maternal grandmother have similar urinary tract anomalies. Physical examination revealed the child to be in the fifteenth percentile for height and third percentile for weight, in no distress. The only positive finding was that of a smooth, firm mass just above the pubis and to the right of the midline. Impression was neoplasm arising in the abdominal

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wall. Urologic work-up revealed a right hydronephrosis on retrograde urography. Complete blood count and urinalysis on admission were not remarkable. At surgery, the tumor was found to involve the rectus muscle and posterior sheath, but not the peritoneum. The midline structures were excised as was the rectus sheath for a distance on the left side as well as the right. The thickened tissues extended down to the symphysis, and they were excised close to the bone and the entire tumor was delivered. Additional pieces of tissue were taken from the edges, superiorly and inferiorly, and were studied microscopically. The superior section showed additional tumor. Additional midline structures in the rectus sheath were excised until no tumor was identifiable. It was possible to preserve some of the rectus muscle on the right and practically all of the rectus muscle on the left. The peritoneum was very thin but intact. The defect, approximately 10 cm. longitudinally and 7 to 8 cm. transversely, was closed in a longitudinal direction. The patient tolerated the procedure well and the postoperative course was uneventful. Microscopic section of the tumor showed well-differentiated spindle-shaped cells separated by a large amount of fibrocollagenous tissue. The cells formed whirl patterns in some areas. Near the periphery of the tumor, the cells were noted to infiltrate muscle. In some areas, regenerated muscle appeared as giant cells. Sections of the anterior rectus sheath showed infiltration by neoplasm except in the superior portion showed only chronic inflammatory reaction. The pathologic diagnosis was desmoid tumor of the abdominal wall. The patient was discharged in good condition on July 24, 1954.

Recurrence was noted in the operative area on Dec. 20, 1955. Respiratory infection delayed further surgical treatment until Jan. 9, 1956, at which time there was a mass 4 by 6 cm. in the area of the old scar. The tissues of the lower abdomen up to and including the umbilicus were thickened and indurated. The previous scar was outlined and excised down to the subcutaneous tissue. The upper and lower skin flaps, covering nearly the entire lower abdomen, were developed, meticulously removing all of the subcutaneous tissues. Specimens were taken for study by frozen section at the umbilicus and each lateral angle of the wound near the anterior superior iliac spines. Desmoid tumor tissue was present in both the umbilical and left angle tissues. The excision was extended in these regions. More than one-half the rectus sheaths and underlying muscles were removed from umbilicus to the symphysis. Tumor lying just above the symphysis was peeled away from the underlying tissue-paper thin peritoneum. The neoplasm was easily delimited on the right, but on the left it invaded the muscle. The entire left posterior sheath of the rectus was removed. The undersurface of the tumor was well encapsulated inferiorly and was separated from the urinary bladder. It was obvious that the recurrence had arisen beneath the symphysis or at its edge and had grown between the symphysis and bladder. A specimen taken from the symphysis showed the tumor was incompletely removed. Removal of the symphysis was not feasible, but could be accomplished later, provided rapid recurrence did not involve the entire area of dissection. The incised edges of the rectus sheath were closed in the midline. In the inferior portion of the wound, especially in the region of the symphysis, it was necessary to make counter incisions laterally into the external oblique sheath to permit it to slide medially. Closure was possible, although under considerable tension. The patient withstood the procedure well and postoperative recovery was uneventful. She was discharged on Jan. 13, 1956, in good condition. Microscopic section revealed the histologic pattern of the tumor to be essentially identical with that from the previous operation. There was extensive, diffuse invasion of fibrofatty and muscular tissue, as well as focal areas of desmoid tumor.

She returned for follow-up evaluation on March 6, 1956. There were no complaints. Examination of the abdomen revealed thickening and induration of the scar tissue, particularly above the symphysis and to the left. There was a firm nodule 1.5 by 1 cm. at the left superior border of the scar area. There was thus evidence of local recurrence and extension. Further satisfactory surgical management was considered virtually impossible.

The pronounced antifibroblastic activity of the glucocorticoid hormones suggested a therapeutic trial using prednisone. Accordingly, the patient was placed on the following regimen of Meticorten, with appropriate ancillary precautionary measures: 10 mg. every 6 hours for 7 days; 7.5 mg. every 6 hours for 4 days; 5 mg. every 6 hours for 6 days; 17.5 mg. a day for one week, then gradual decrements of 2.5 mg. until a daily dosage of 5 mg. was reached on May 2, 1956. Response to this therapy was spectacular. Within 3 weeks, the nodule had disappeared and the lower abdominal wall had perceptibly softened. The lower abdominal wall became progressively softer and more pliable until by May 2, 1956, there was no thickening or induration. She has continued to take 5 mg. prednisone daily and has thrived, having exhibited satisfactory growth and development. There have been no complications associated with steroid therapy, but there is a minimal "Cushingoid" appearance.

DISCUSSION

Since recurrence was prompt following the initial operation and since the neoplasm was incompletely removed at the time of the second operation, it was virtually certain that recurrence would be fairly rapid, and it was. For this reason, biopsy of what was assumed to be a second recurrence was not done. It is known that desmoid tumors, as had twice previously been illustrated in this patient, enlarge progressively and infiltrate surrounding tissues. Spontaneous regression has not been reported. The disappearance of the nodule and the thickening and induration of the abdominal wall directly followed the institution of prednisone therapy and correlates so well with the expected effect of glucocorticoid hormone on fibroblastic tissue that there seems to be little doubt that the improvement noted was due to the action of this hormone. The failure of recurrence after 3 years on maintenance therapy is impressive. Booher and Pack have reported the use of ACTH over a 6-week period without significant improvement in a 14-year-old boy. This patient's original tumor had appeared above the left groin at the age of 4 years. The subsequent course is illustrative of the difficulties and complications associated with the management of this neoplasm. He underwent a total of four extensive operative procedures, five courses of irradiation, one 10-week course of antimetabolite ("teropterin"), implantation of gold-filtered radon seeds, a course of large doses of vitamin E, intramuscular injections of large doses of methyl testosterone, and, finally, a 6-week course of ACTH. Approximately 6 months later, following a second episode of intestinal obstruction and peritonitis secondary to progressive tumor infiltration, the patient expired, 8 years after the first excision of the tumor.

The encouraging results obtained in the subject of this report prompt the recommendation of further trial of this type of therapy in patients in whom surgical management is not feasible.

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RECURRENT GASTRIC HEMORRHAGE DUE TO IDIOPATHIC HEMORRHAGIC GASTRITIS WHICH REQUIRED TOTAL GASTRECTOMY

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ALTHOUGH upper gastrointestinal bleeding is usually diagnosed as due to peptic ulcer, esophageal varices, or one of several other demonstrable lesions, there are a large number of cases (up to 40 per cent) which, after all diagnostic tests are exhausted, are still undiagnosed. With the development of surgical treatment for upper gastrointestinal hemorrhage, it has been felt that minute ulcerations have been a cause for the bleeding in certain cases.[4] Very little has been said about "gastritis." We have recently seen 3 cases of idiopathic hemorrhagic gastritis with massive hemorrhage, 2 of which were explored initially and no pathology was found. A partial gastrectomy was done as is frequently recommended.[1, 4, 6] In all 3 cases bleeding stopped but recurred several days later on an increased scale and was solved only by total gastrectomy.

CASE REPORTS

CASE 1.†—A 31-year-old white woman was admitted to the 97th General Hospital, Frankfurt, Germany, on Dec. 18, 1956, in early labor. She delivered spontaneously a normal female infant weighing 8 pounds, after a labor of 20 hours, 40 minutes. There was no past history of serious illness, gastrointestinal disturbance, or unusual salicylate ingestion. Postpartum course was uneventful with no excessive vaginal bleeding. Routine postpartum hemoglobin on December 22 was 8.5 grams and the patient was given 500 c.c. of whole blood. Several hours later she complained of dizziness, weakness, and had several large tarry stools. Examination revealed the patient to be very pale and perspiring freely. Blood pressure was 110/70 mm. Hg, and the pulse 140 and of poor quality. Large amounts of bright red blood were also obtained via Levine tube. Hemoglobin was 3.8 with hematocrit of 12. Laboratory studies revealed no disturbance of the clotting mechanism and no evidence of blood dyscrasia. The patient was immediately given 6 units of whole blood rapidly with only moderate improvement. She remained pale, restless, and the pulse rate remained 140, although blood pressure never went below 110 systolic. Twelve units of blood was required; therefore, laparotomy was performed. The entire gastrointestinal tract was seen to contain blood. No ulcer was palpable in the stomach or duodenum. The liver appeared normal. No varices were evident. It was decided to perform a partial gastrectomy because of the massive bleeding which was obviously originating either from the stomach or duodenum. The duodenum was divided just below the pylorus. The duodenal mucosa appeared normal, and there was no ulcer. The mucosa of the stomach was moderately injected, but no bleeding point was visualized. A 70 per cent Billroth I gastrectomy was performed. The patient's condition immediately improved, and stabilized following surgery. Her postoperative course

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†Case reported previously by us.[2]

was completely uneventful, and she was placed on a liquid diet on the fourth postoperative day. On December 29 (sixth postoperative day), the patient had sudden massive hematemesis and melena. She was transfused and her general condition appeared to improve for a period of 6 to 8 hours, and it was felt that the bleeding had ceased. However, there was recurrent hematemesis of massive proportions, and on December 31, after rapid blood transfusion through two portals, operation was again performed. The entire stomach mucosa was seen to be fiery red and diffusely bleeding. No muocsal ulcerations were noted. The remainder of the stomach, except a small cuff, was resected. The bleeding from this cuff of stomach ceased after packing it for approximately 10 minutes with a laparotomy pad, and the patient's vital signs rapidly improved. We were reluctant to perform total gastrectomy; and since bleeding appeared to be controlled, a posterior Polya anastomosis was performed. During this second episode, 40 units of blood was given.

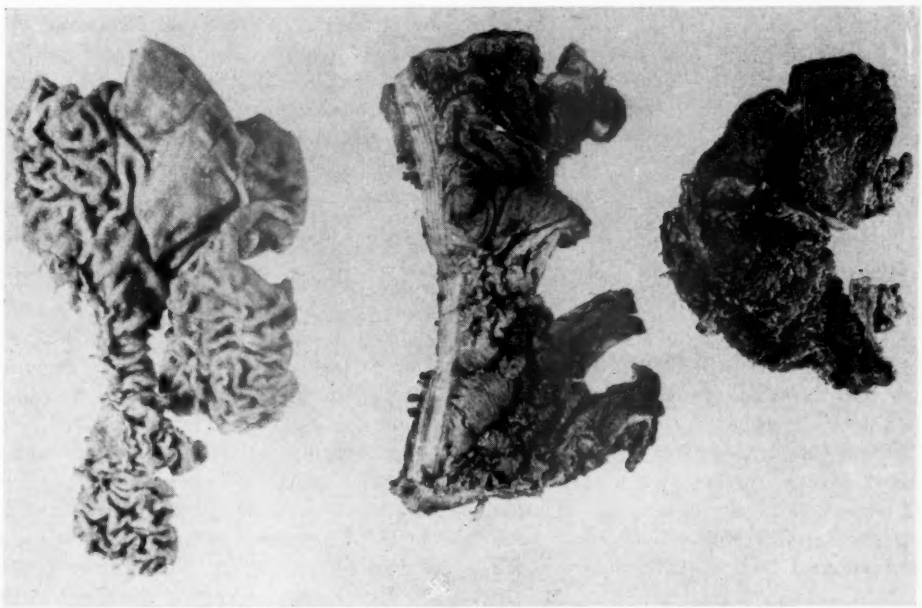

Fig. 1.—Case 1. At *left* is stomach removed at first operation. The mucosa is grossly normal. In the *center* is the stomach removed at the second operation. The mucosa is moderately hemorrhagic. At the *right* is the gastric remnant removed at the third operation. The mucosa is extremely hemorrhagic.

The patient had a benign postoperative course until January 4 (fourth postoperative day) when she again had sudden massive hematemesis with shock. She was again transfused (11 units of blood) and reoperated upon. The gastric mucosa was markedly hemorrhagic and bleeding from its entire surface (Fig. 1). A total gastrectomy with a Roux-en-Y esophagojejunostomy was performed. The patient improved rapidly following gastrectomy and tolerated frequent small feedings well. She was discharged from the hospital 5 weeks after admission on a diet of at least 2,000 calories daily, vitamin B_{12} injections biweekly, plus pancreatin for mild fat intolerance. She has maintained her weight at 114 pounds and has shown no evidence of "dumping" syndrome or anemia. Total proteins and blood chemistries have been normal.

Pathology Report.—The three resected specimens showed grossly a progressive increase in the degree of mucosal hemorrhagic involvement. No ulceration or tumor was present (Fig. 1). Microscopically, all specimens revealed hemorrhage in the mucosa and submucosa with edema. The muscularis was infiltrated with granulocytes. Blood vessels showed no parietal alteration or thrombi. Elastic stains were normal.

Case 2.—A 40-year-old, short, obese, white man was admitted to the U. S. Army Hospital, Berlin, Germany, on July 20, 1957, with massive upper gastrointestinal bleeding as

evidenced by frequent black stools and fainting. After 40 units of whole blood replacement, an emergency gastrectomy (anterior Polya) was performed. No bleeding point was found, and the stomach was reported normal. Postoperatively his condition was good, and there was no more bleeding. Four days later the abdominal wound dehisced with evisceration. This was repaired with wire retention sutures. Five days later massive hemorrhage began again with both hematemesis and melena. There were severe asthma and lung congestion. One of us (R. M. H.) was called from Frankfurt, Germany, at this point to see the patient. Esophagoscopy and gastroscopy were carried out by Lieutenant Colonel Eddy Palmer which showed severe, actively bleeding, erosive gastritis over the entire gastric remnant. A total gastrectomy was carried out. Seventy-six units of blood was given during this second bleeding episode and surgery. During the procedure, there was profuse oozing of blood from all surfaces. Calcium, vitamin K oxide, vitamin C, and fibrinogen were given in large amounts. The immediate postoperative course was relatively good, the patient remaining out of shock for the first time since the recurrent bleeding. Asthma was improved. Urine output was fairly good (750 c.c.) but it contained hemoglobin. Two days later the patient was flown out of Berlin to the U. S. Army Hospital, Landstuhl, Germany. He developed pulmonary edema on the plane but this was quickly controlled. However, after transfer, the patient's urinary output was only a few cubic centimeters and he died on the fourth postoperative day. Autopsy showed multiple small abscesses of the pancreas associated with a leak in the duodenal stump and lower nephron nephrosis.

Pathology Report.—First operation: Generalized moderate chronic gastritis without ulceration. Second operation: Marked hemorrhage with diffuse chronic inflammation and focal areas of superficial erosion.

CASE 3.—A 34-year-old white woman was admitted to the 97th General Hospital, Frankfurt, Germany, on Sept. 19, 1957, with profuse upper gastrointestinal hemorrhage as evidenced by vomiting blood and passage of bloody stools. She received 4 units of blood. The bleeding stopped, and she appeared much improved. However, 4 days later massive bleeding recurred. She had another transfusion (11 units of blood) and was operated on. The entire stomach was lined with a hypertrophic hemorrhagic mucosa which seemed to be weeping blood everywhere, especially near the cardia. It was decided to do a total gastrectomy inasmuch as partial gastrectomy would not excise much of the bleeding area. The postoperative course was complicated by a leak at the site of the anastomosis. However, she recovered and was discharged on the twenty-third postoperative day. There was no further bleeding. She has done well since surgery, maintaining her weight and being active as a housewife.

Pathology Report.—Severe hemorrhage in mucosa and submucosa with edema (Fig. 2).

DISCUSSION

None of the 3 patients had had any gastrointestinal symptoms before the present illness. Two of the patients showed initially a massive hemorrhage from the upper gastrointestinal tract with negative findings at surgery (and x-rays); both appeared to respond to partial gastrectomy. All 3 had recurrent massive hemorrhage and only stopped bleeding when the entire stomach was removed. The stomach at the second and third operations showed progressive changes from normal mucosa to massive mucosal and submucosal hemorrhage with some necrosis (Fig. 1). The reason for this dramatic progress in severity of bleeding is obscure, but there are several possibilities:

Stress.—It is well known that stress may cause gastric ulceration and hemorrhage. Such clinical entities as Curling's ulcer after burns and other trauma and ulceration after cortisone therapy are examples. Mental stress is thought to produce peptic ulceration and has been shown to cause a marked gastric mucosal injection. All 3 of these patients had abundant stress.

Transfusion Reaction.—It has been shown[8, 9, 13, 15] that hemorrhage into the gastrointestinal tract with superficial necrosis of the mucosa can be produced in dogs as a result of microscopic thrombi in the submucosal capillaries produced by an incompatible transfusion given intra-aortically. Usually this involves the

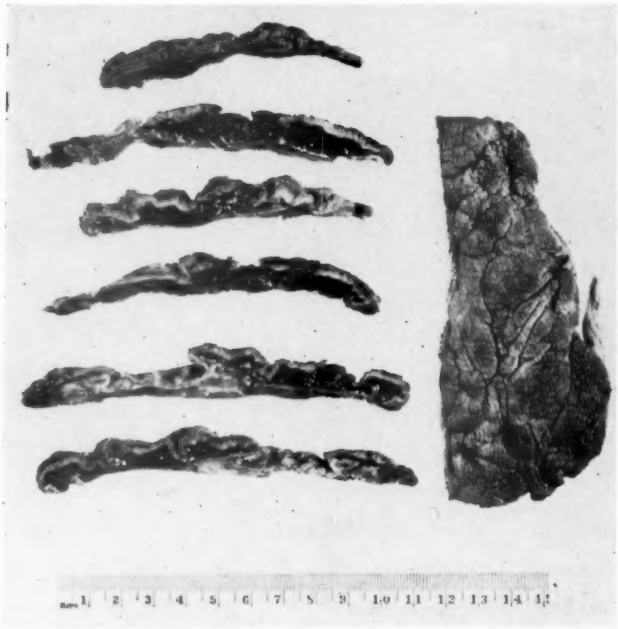

Fig. 2.—Case 3. Sections of stomach removed showing gross mucosal and submucosal hemorrhage.

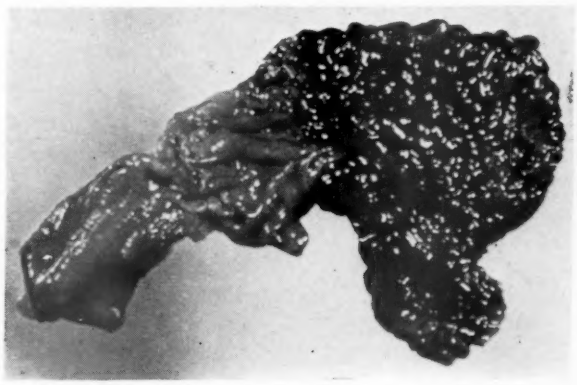

Fig. 3.—Stomach and first part of duodenum of dog which was given an incompatible transfusion into the aorta. Note the hemorrhagic fundus but relatively normal antrum and duodenum.

intestine but may also involve the stomach and in one instance was localized to the fundus of the stomach (Fig. 3). This dog died in shock after vomiting blood for 2 days. It is known also, that a hemorrhagic diathesis frequently develops after a transfusion reaction. This may manifest itself by gastrointestinal tract hemorrhage.[7, 8, 12, 13]

This bleeding tendency is due in part to an intravascular clotting episode with resulting afibrinogenemia due to using up of fibrinogen[7] and to the appearance of a heparin-like anticoagulant in the blood.[12] There also may be activation of fibrinolytic enzymes.[7] No diagnosed transfusion reaction occurred in any of these cases. However, so many transfusions were given that some

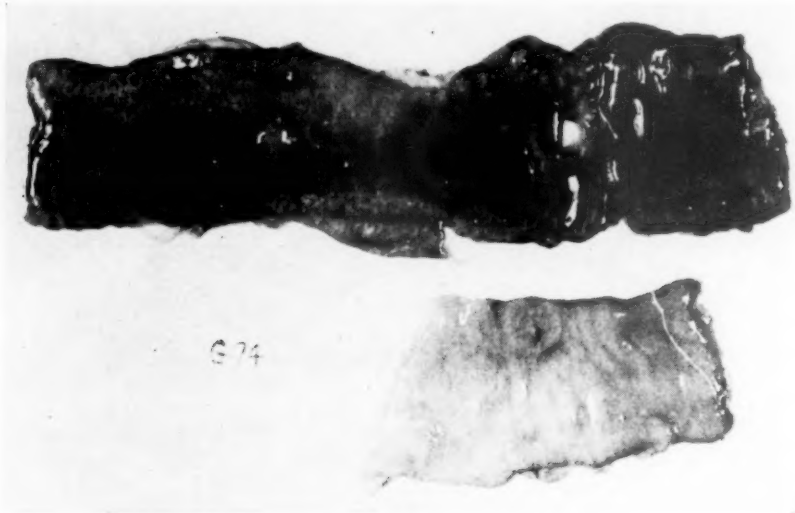

Fig. 4.—At the *top* is the duodenum of a dog which died in shock produced by intra-aortic transfusion of human blood. Note the marked hemorrhage in the mucosa as compared with a piece of ileum from the same dog (*below*).

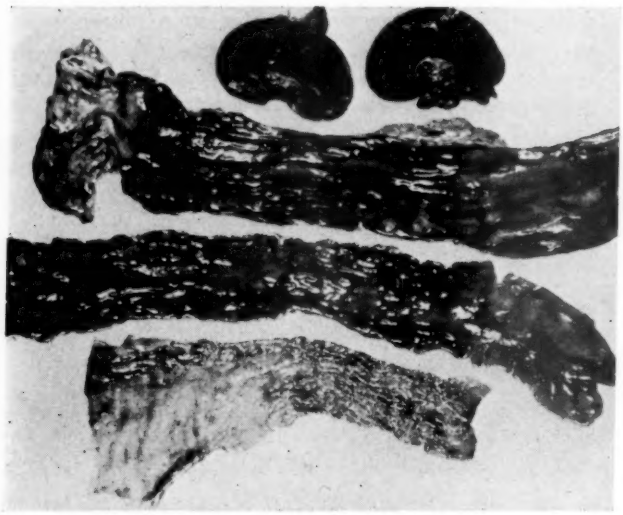

Fig. 5.—Kidneys (*above*), small intestine (*middle*), and large intestine (*below*) of a dog which died in shock after an intra-aortic transfusion of human blood. Note the marked hemorrhage of the mucosa of the small bowel and relatively minor hemorrhages in the large bowel.

minor incompatibilities are certainly possible. It is known also that massive transfusions are frequently accompanied by a bleeding tendency. This may be due to minor incompatibilities or citrate intoxication.[16] There is a drop in platelets and fibrinogen which may play a part.

Prolonged Surgery.—It has been noted that prolonged surgery, particularly chest operations, may result in a bleeding tendency. This may be due to production of fibrinolysins or depletion of fibrinogen by large scale clotting.

Trauma.—It has been shown that a crush injury results in activation of fibrinolytic enzymes, a decrease in platelets, and the appearance of circulating anticoagulant.[14] Trauma and surgery have been known to produce peptic ulcers which require surgery.[3, 5] Some of these have taken the form of multiple punctate ulcers with weeping of blood by the entire gastric mucosa. There had been previous surgery in 2 of the present cases (two operations within one week).

Shock.—It has been shown that shock is associated with a hemorrhagic necrosis of the gastrointestinal mucosa.[9, 10, 11, 13] All of these patients had been in shock and this is a most interesting possibility. Fig. 4 shows a dog's duodenum after shock due to an incompatible transfusion. Fig. 5 shows the small intestine of another. Apparently this type of hemorrhagic necrosis is due to capillary thrombosis of the mucosa and the submucosa.[9, 13] The process is accompanied by activation of fibrinolysins which may explain why thrombi are not usually found in clinical autopsy material. The so-called intestinal factor[10, 11] in shock is a proved entity, but its true significance has not yet been established.

SUMMARY

1. Three cases of massive gastric hemorrhage due to idiopathic hemorrhagic gastritis which appeared to progress after transfusion and/or surgery are presented. Total gastrectomy was necessary to control the hemorrhage.

2. The initial cause of the bleeding is unknown.

3. Several possible causes of the recurrent bleeding are discussed. These include: (a) stress factor, (b) transfusion reaction, (c) prolonged surgery, (d) trauma, and (e) shock. The latter four of these factors all concern intravascular clotting and the blood clotting defects which accompany it.

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SPONTANEOUS HEMORRHAGIC RUPTURE OF THE KIDNEY ASSOCIATED WITH PERIARTERITIS NODOSA

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RUPTURE of the kidney with retroperitoneal hemorrhage is most often the sequel of external trauma. Occasional cases of spontaneous rupture of the kidney have been reported with no antecedent history of traumatic injury. Pathologic study of these cases has usually revealed a congenital anomaly or an obstructing uropathy predisposing to rupture.[2] An even rarer cause of spontaneous kidney rupture and massive retroperitoneal hemorrhage is involvement of the kidneys with periarteritis nodosa. In the past 5 years, 2 patients with periarteritis nodosa and renal rupture with massive hemorrhage have been studied or treated at this institution. One patient presented an interesting problem in the diagnosis and management of spontaneous massive retroperitoneal hemorrhage. The other patient died 2 hours following the onset of left flank pain. Because of the rarity of this difficulty, it is thought advisable to report these cases and to review the pertinent literature.

CASE REPORTS

CASE 1.—The patient was a 36-year-old white male mechanic who was admitted on Feb. 12, 1958, because of excruciating left flank pain suffered while driving his automobile; it subsided after 10 minutes. Several hours later, the pain recurred and was even more intense. It radiated from the left costovertebral angle into the left inguinal region. The patient was hospitalized for 3 days and treated with analgesics with the presumptive diagnosis of renal colic. He failed to improve and was referred for management.

The past history was significant in that there had been several previous hospitalizations in our institution for conditions related to hypertension known to have been present since 1948. In June, 1957, the significant findings were a blood pressure of 230/160 and old fundal exudates and hemorrhages. The hemogram was normal. The urine showed a specific gravity of 1.018, a trace of albumin, and an occasional white blood cell. The blood urea nitrogen was 19 mg. per cent. An intravenous pyelogram was normal. The Regitine test for pheochromocytoma was negative. The patient was treated with a low salt diet, phenobarbital, and Serpasil, with amelioration of dyspnea, but with little change in the elevated blood pressure. Inversine was administered without appreciable effect. He left against medical advice and was readmitted in January, 1958, because of dyspnea, ankle edema, and abdominal swelling. The blood pressure was 234/170 and there was papilledema with narrowing of the arterioles. The blood urea nitrogen was 20 mg. per cent. Treatment with a 500 mg. sodium diet, digitalis, mercurial diuretics, and 1.0 mg. Inversine three times a day resulted in a 30-pound weight loss and subjective improvement. However, the blood pressure continued to range from 180 to 270 mm. Hg systolic and from 110 to 180 mm. Hg diastolic. He left the hospital 2 weeks before his final admission.

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At this time, physical examination revealed the blood pressure to be 96/76; pulse 116; temperature 100.4° F.; respirations 30. The patient appeared pale, acutely ill, and anxious. The point of maximum cardiac impulse was in the left fifth intercostal space of the anterior axillary line. The abdomen was asymmetrically distended with a marked protuberance of the left flank and left upper quadrant. A large poorly circumscribed mass filled the left flank and extended along the left lateral abdominal wall to the region of the left inguinal ligament. There was spasm of the left lateral abdominal muscles and exquisite tenderness of the left flank. Peristaltic sounds were hypoactive. The right side of the abdomen was soft and nontender.

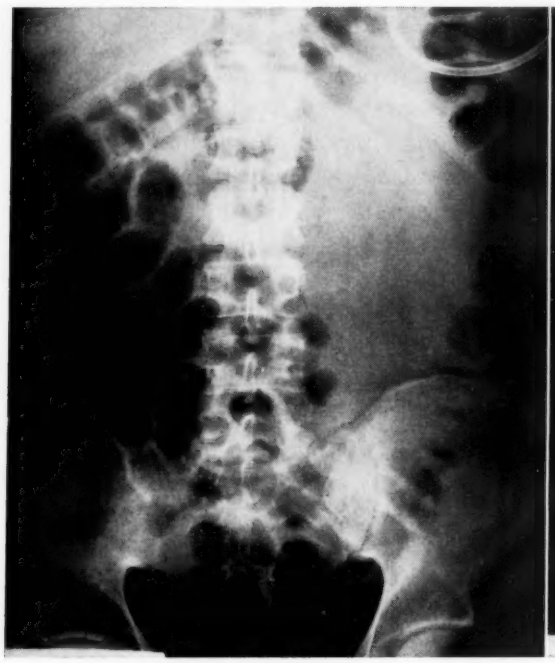

Fig. 1.

Fig. 2.

Fig. 1.—A preoperative x-ray of the abdomen in Case 1 reveals displacement of the intestines to the right side by a large left abdominal mass. There is evidence of paralytic ileus.

Fig. 2.—Retrograde urogram performed preoperatively in Case 1 discloses medial shift of the left ureter.

Laboratory examination revealed a hemoglobin of 6.2 Gm. per cent, white blood count 28,500, with 83 per cent polymorphonuclear leukocytes. Urinalysis showed a specific gravity of 1.008, albumin 3 plus, and sugar 1 plus. Microscopic examination of the urine disclosed 40 to 50 red blood cells per high-power field and numerous granular casts. An intravenous pyelogram showed normal visualization of the right kidney, and no definite visualization of the left. A large mass filled the left retroperitoneal gutter (Fig. 1). A retrograde pyelogram disclosed deviation of the left ureter medially (Fig. 2). During the next 12 hours, the patient was transfused with 2 L. of blood and the hemoglobin rose from 6.3 to 8.5 Gm. Under general anesthesia, exploration of the left retroperitoneal area was performed. Preliminary to this, a left thoracotomy through the seventh intercostal space was carried out and the descending thoracic aorta was secured with tapes as a precaution in case active bleeding was still present. About 4 pints of fluid and clotted blood was removed from the retroperitoneal area. A transverse rent in the lower pole of the left kidney was discovered which measured about 2 cm. in length. The kidney was of normal size and had a finely granular surface. A small segment at

the site of the laceration was removed for microscopic study. The lacerated edges were approximated with mattress sutures of chromic catgut. The retroperitoneal space was drained, and the chest and flank incisions were closed.

The procedure was well tolerated, and the patient was making a satisfactory recovery until the fourth postoperative day when brisk bloody drainage was noted from the flank incision. The blood pressure declined from 170/110 to 118/90. Two liters of blood was administered, and on the following day the bleeding abated. There was progressive improvement, and 3 weeks postoperatively the patient was transferred to the medical service for re-evaluation and treatment of the hypertension. A pericardial friction rub was noted and evidence of pericardial effusion was seen on chest x-ray. The blood urea nitrogen ranged from 30 to 33 mg. per cent. The venous pressure was 180 mm. of saline with elevation on exercise to 280 mm. The arm-to-tongue circulation time was 22 seconds. The patient complained of left thigh pain and discomfort, which was thought, at first, to be related to psoas irritation, secondary to the retroperitoneal hemorrhage. A segment of skin and muscle from the left thigh was removed for study and revealed lymphocyte and plasma cell infiltration of the walls of the arterioles and venules. There was medial hypertrophy of the arterioles. On March 22, Inversine therapy was started, and the dosage was increased progressively to 3.75 mg. every 6 hours. Diuril, a 500 mg. sodium diet, digoxin, and cortisone were administered. The blood pressure continued to be about 240/140. There was progressive deterioration of the mental status with episodes of confusion and boisterousness. The patient's weight declined from 170 to 115 pounds. He became disoriented and died on May 16.

The original kidney biopsy showed severe changes in the arterial and arteriolar vessels with medial hypertrophy and narrowing of the lumina. No fibrinoid or inflammatory changes of the vessels were noted in this specimen. The original pathologic diagnosis was, therefore, arterial and arteriolar nephrosclerosis.

Postmortem examination revealed right lower lobe pulmonary infarction, right empyema, and marked left ventricular hypertrophy. The small intestinal mesentery, testis, liver, and right kidney were the site of thrombosed medium-sized and large arteries which showed fibrinoid necrosis, intramural hemosiderin deposits, and eccentric fibrosis of the arterial wall characteristic of periarteritis nodosa (Figs. 3 and 4). Some of the involved vessels showed evidence of acute inflammation.

Summary.—This 36-year-old white man who had been known to have hypertension for 10 years with severe acceleration of the hypertension for one year entered the hospital with left flank pain of sudden onset and evidence of massive retroperitoneal hemorrhage and shock. There was no antecedent trauma. A rupture of the lower pole of the left kidney with hemorrhage into the retroperitoneal space was discovered at operation, and the laceration was repaired. The patient recovered only to succumb 3 months later with evidence of severe hypertension and mental confusion. Renal biopsy at operation showed arterial and arteriolar nephrosclerosis. Skin and muscle biopsy revealed nonspecific vasculitis. The final diagnosis at postmortem examination was periarteritis nodosa involving many organs.

CASE 2.—The patient was a 32-year-old white farmer who was admitted to the hospital on Sept. 1, 1953, because of headaches and high blood pressure. He had been well until 4 months prior to admission when he noted the gradual onset of frontal headaches in the morning. One month before admission, nausea and vomiting occurred in association with the headaches. He bruised easily. A diagnosis of hypertension was made, and he was treated with antihypertensive drugs and intravenous fluids. There was little improvement. There were no history of renal disease and no symptoms of congestive heart failure.

Physical examination revealed a cooperative white man who did not appear to be ill. His responses were slow. There were numerous old ecchymotic areas on the legs and abdomen. The blood pressure was 288/142; temperature 99.8° F.; respirations 26; pulse

Fig. 3.

Fig. 4.

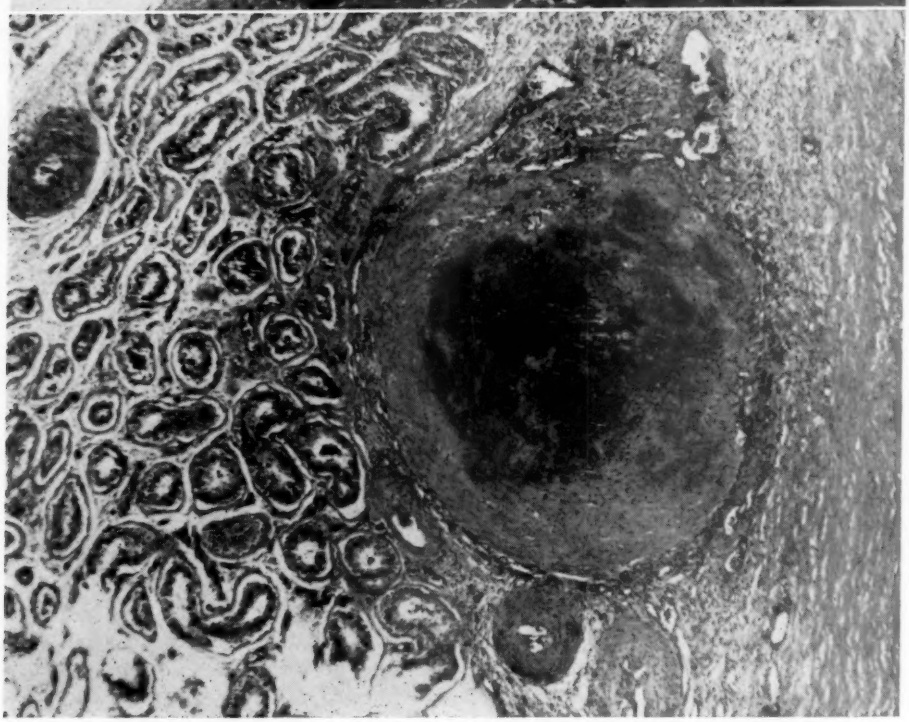

Fig. 3.—A section of the right kidney in Case 1 shows thrombotic occlusion of an artery in the lower half of the photomicrograph. There are fibrosis of the vascular wall and hemosiderin depositions. (×100; reduced 1/20.)

Fig. 4.—A section of testis in Case 1 reveals a moderate-sized artery in the tunica albuginea with an advanced lesion of periarteritis nodosa. There are thrombosis, recanalization, and hemosiderin deposition in the wall of this artery. (×100; reduced 1/20.)

96. Bilateral papilledema and fundal hemorrhages and exudates were noted. The point of maximum cardiac impulse was 12 cm. to the left of the mid-sternal line. The remainder of the physical examination and the neurologic examination were within normal limits.

Laboratory examination showed a hemoglobin of 13.5 Gm.; leukocyte count 4,200; neutrophils 77 per cent, lymphocytes 14 per cent, monocytes 9 per cent. The urinalysis revealed a specific gravity of 1.016, 1 plus albumin, sugar negative, 46 white blood cells per high-power field. Urine culture was negative. Blood urea nitrogen was 52 mg. per cent; creatinine 3.3 mg. per cent. The prothrombin time was 59 per cent of normal; platelets 390,000 per cubic millimeter.

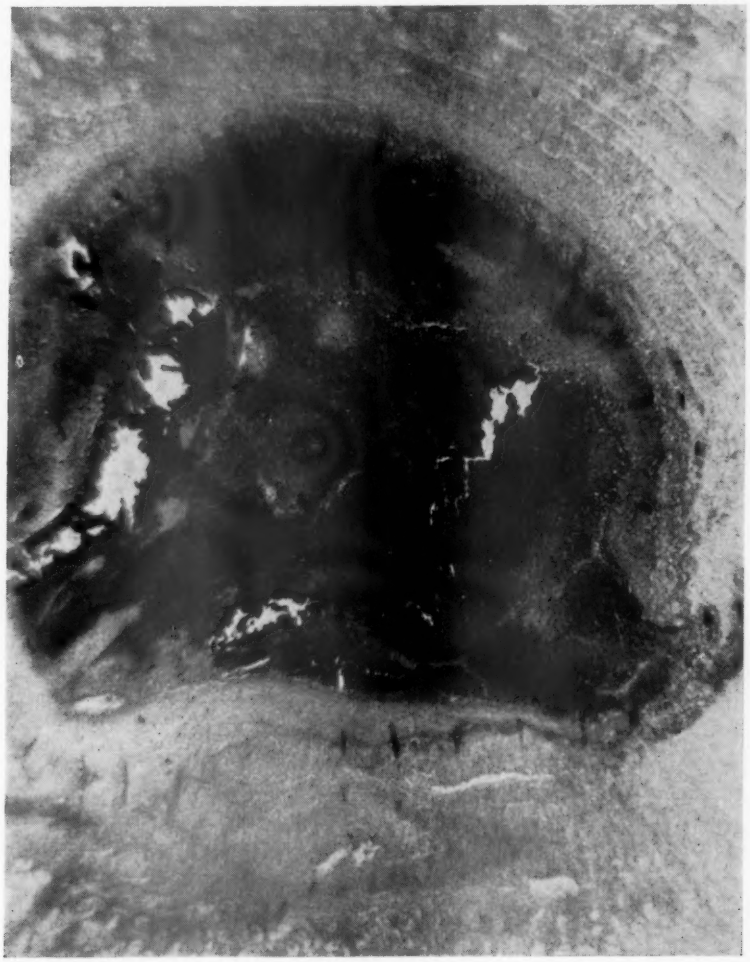

Fig. 5.—A section of the ruptured artery of the left kidney in the second patient reveals aneurysmal dilatation of the vessel with hemorrhage into the wall. There are intramural fibrinoid necrosis and focal collections of polymorphonuclear leukocytes. (×30.)

A chest x-ray showed left ventricular enlargement.

The total hospital stay was 16 days, and the patient remained afebrile throughout. The blood pressure was recorded twice daily and varied between 165/110 and 230/175. The benzodioxane test was negative for pheochromocytoma. An Amytal sodium sedation test produced no lowering of the blood pressure with sleep. The clinical impression was that of hypertensive vascular disease in the accelerated or malignant phase with hypertensive encephalopathy manifested by marked lethargy and occasional confusion

with incoordination. The patient was treated with a 200 mg. sodium diet and phenobarbital, 30 mg. four times a day. On September 17 at 3:00 A.M., the patient awoke from sleep and complained of sudden left flank pain. Analgesics ameliorated the pain. Two hours later the patient died.

Postmortem examination revealed 1,500 c.c. of blood in the left retroperitoneal area and a small rent (measuring 4 by 0.5 cm.) of the posterolateral border of the kidney in its mid-portion. This kidney weighed 200 grams and the right 180 grams. Their surfaces were mottled with yellow and tannish-pink areas. Scattered petechiae were seen on the surface of the right kidney. A probe inserted into the rent of the left kidney passed into a ruptured blood vessel at the corticomedullary junction. The corticomedullary junction was distinct.

Microscopic study of the kidney revealed fibrinoid change with polymorphonuclear leukocyte infiltration of afferent glomerular arterioles and focal fibrinoid change of the glomerular capillaries. Medium-sized arteries showed focal fibrinoid change, and a section of the ruptured artery revealed fibrinoid necrosis of the wall (Fig. 5).

Small arteries in the esophagus, stomach, pons of the brain, pineal gland, gall bladder, adrenal gland, and thyroid gland showed areas of fibrinoid necrosis with infiltration of the vessel wall with neutrophilic and eosinophilic polymorphonuclear leukocytes and lymphocytes (Figs. 6 and 7). In other areas there was intramural infiltration with plasma cells and lymphocytes. A small serosal artery of the stomach was thrombosed, and there was hemosiderin deposition in macrophages in the wall. Periarterial infiltration of eosinophils and lymphocytes was present.

Summary.—After a 4-month history of severe hypertension for which he was being studied and treated, this 32-year-old farmer suddenly developed left flank pain and died 2 hours later. There was no previous history of trauma, and he had been constantly observed in the hospital for 2 weeks.

Postmortem examination revealed a local rupture of the left kidney with massive retroperitoneal hemorrhage. An artery of moderate size at the corticomedullary junction with fibrinoid necrosis of the wall communicated with the retroperitoneal area. There was focal fibrinoid change and inflammation of the afferent glomerular arterioles and small arteries of the kidneys. Fibrinoid changes with inflammation were noted in many small and medium-sized arteries in many organs throughout the body, characteristic of periarteritis nodosa.

DISCUSSION

The 2 patients presented were considered to have malignant hypertension which was refractory to antihypertensive drug therapy. In each case, an acute episode occurred, heralded by the sudden onset of flank pain and characterized by hemorrhagic shock in the first patient and rapid death in the second patient.

In the first patient, the preoperative differential diagnosis included massive retroperitoneal hemorrhage from a ruptured aortic aneurysm, spontaneous rupture of the kidney, rupture of the spleen, and hemorrhage from a renal or retroperitoneal neoplasm. Because there were clinical signs of continuous retroperitoneal bleeding, surgical exploration of the retroperitoneal space was performed as an emergency procedure. Hemostasis was quickly obtained by suture of the ruptured kidney; the thoracic aorta had been isolated in case its immediate temporary occlusion was necessary.

Three cases of ruptured kidney associated with periarteritis nodosa have been previously reported.[3, 4, 7] Wever and Perry[7] mentioned this occurrence in a 29-year-old white man who had had hypertension for 7 years. Anemia and a right flank mass were present for 13 days before nephrectomy was performed. He did not survive long. Harris and Friedrichs[3] reported the death of a 32-year-old man resulting from renal hemorrhage into the retroperitoneal

Fig. 6.

Fig. 7.

Fig. 6.—The gall bladder in Case 2 is the site of acute and chronic vascular changes typical of periarteritis nodosa. The central vessel in the muscularis shows the most intense intramural and periarterial infiltration of polymorphonuclear leukocytes. Fibrinoid change is evidenced by the deep homogeneous quality of the vascular wall. (×30; reduced 1/20.)

Fig. 7.—A serosal artery of the stomach in Case 2 is occluded by fibrous tissue and shows hemosiderin deposition. There are scattered polymorphonuclear leukocytes and lymphocytes in its wall. (×100; reduced 1/20.)

space. Herbut and Price[4] described a 30-year-old man with hypertension, who developed severe right lumbar pain and died of a large retroperitoneal hemorrhage. In each of these 3 cases, it was possible to identify rupture of the kidney and of a medium-sized artery involved with a typical lesion of periarteritis nodosa. The arteries of many other viscera also showed inflammatory and fibrinoid changes.

Periarteritis nodosa is one of a group of the so-called "collagen diseases." This arbitrary pathologic classification merely denotes the common findings of connective tissue alterations characterized by fibrinoid necrosis. In most pathologic studies, the kidney has been the site of the most frequent and profound morphologic changes. Rose[6] has reported that 79 per cent of patients with periarteritis show renal involvement, and Allen[1] has also noted kidney lesions in 70 to 80 per cent of cases. Clinically, renal disease may be manifested by hematuria, mild or malignant hypertension, renal insufficiency, or spontaneous rupture of the kidney with massive retroperitoneal hemorrhage. The massiveness of the hemorrhage in the 3 cases previously reported in the literature and in the 2 which we observed may be related to the fibrinoid necrosis and inflammation of the arterial wall. This produces destruction of the elastic laminae and aneurysmal dilatation of the vessel. The artery is rendered incapable of effective contraction once rupture occurs. Since severe hypertension is often present, little time may elapse before exsanguination and death occur.

The incidence of periarteritis nodosa is greater in men than in women, and the average age at the time of diagnosis is about 41.5 years.[5] The 2 male patients reported upon here were 36 and 32 years of age, and the 3 men in previous reports were 29, 32, and 30 years of age. Approximately 20 per cent of all cases with renal involvement by periarteritis nodosa show malignant hypertension.[6] Four of the 5 patients with ruptured kidneys and periarteritis had evidence of marked elevation of blood pressure. In one of the 2 cases reported here, skin and muscle biopsy gave a clue that we were dealing with periarteritis nodosa. Since the characteristic vascular lesions in this disease are of a focal nature, random biopsy may be negative. In fact, only approximately 42 per cent[5, 6] of cases have been diagnosed by skin and muscle biopsy. The presence of a tender nodule in the subcutaneous tissue of an extremity may aid in pinpointing the area which should be biopsied.

Though renal involvement in cases of periarteritis is very frequent, judging by the paucity of reports, spontaneous rupture with fatal or life-endangering retroperitoneal hemorrhage must be rare. From a review of our own 2 cases and the 3 others described in the literature, it would appear that this occurrence is grave, indeed. All 5 patients were dead within a relatively short period of time. When confronted with the problem of rupture of the kidney and massive hemorrhage, however, one should make every effort to stop the bleeding. Since periarteritis nodosa most often involves both kidneys, treatment should be aimed at conserving as much of the renal tissue as possible.

The course of the disease process of periarteritis nodosa is not altered in any way, but immediate death due to retroperitoneal exsanguination may be averted by surgery.

SUMMARY

Two cases of periarteritis involving the kidneys and associated with spontaneous rupture have been described. Three cases recorded in the literature have been reviewed. The treatment of this hazardous complication should be aimed at stopping the hemorrhage and saving as much renal tissue as possible. Such efforts may avert death from exsanguination, but cannot be expected to alter the course of the underlying disease.

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POSTOPERATIVE COMPLICATIONS DUE TO STAPHYLOCOCCUS AUREUS

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INTRODUCTION

POSTOPERATIVE septic complications which are due to *Staphylococcus aureus* are not new. However, since the advent of antibiotics there has been a gradual emergence of staphylococcic strains which are penicillin-resistant. Strains resistant to other antibiotics are also frequently encountered. The problem of antibiotic-resistant hospital organisms is widely appreciated at the present time, and this problem has been a source of major difficulty in some hospitals. The purpose of this paper is to review the staphylococcal complications on the surgical service of The John Sealy Hospital, Galveston, Texas, from Jan. 1, 1955, to Oct. 1, 1958.

METHODS AND MATERIALS

A review of all patients operated on in The John Sealy Hospital by the general surgical service and the surgical specialties, during the period of time just stated, has been made. This study includes both charity and private cases. Excluded from this study are patients admitted with abscesses which were drained, or furuncles and abscesses drained by the surgical staff on medical service patients, since these do not represent true postoperative complications. Also, excluded from this study are the patients with burns. Burns are a special problem due to the large contaminated open wounds in which *Staphylococcus aureus* is frequently present.

Excluding these types of cases, there have been 65 complications (total) in 55 patients. An analysis of these cases constitute the material for this report.

CASES AND RESULTS

Wound Infections.—The types and number of postoperative complications due to *Staphylococcus aureus* are recorded in Table I. The 34 wound infections recorded in Table I occurred in clean operative cases. In all 34 wound infections except one, the infection responded to simple incision and drainage and resulted in minimal morbidity. In this one instance, an infection in an inguinal hernia incision continued to drain for 12 months and required two subsequent wound explorations to remove infected sutures.

A breakdown of anatomic regions in which the 34 postoperative wound infections occurred is shown in Table II. The circumcision infections are listed

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TABLE I. NUMBER AND TYPES OF POSTOPERATIVE STAPHYLOCOCCAL COMPLICATONS WHICH HAVE BEEN ENCOUNTERED IN THIS HOSPITAL DURING THE TIME PERIOD COVERED BY STUDY

Wound infections	34
Furuncles	12
Parotitis	3
Peritonitis	1
Peritoneal abscess	1
Bacteremia and septicemia	5
Osteomyelitis	2
Meningitis	2
Abdominal wall abscess	1
Brain abscess	1
Pneumonia	3
Total	65

TABLE II. ANATOMIC LOCATION OF THE STAPHYLOCOCCAL WOUND INFECTIONS

Head and neck	4
Trunk*	23
Circumcision	2
Extremities	5
Total	34

*Two of the infections of the trunk were infections of circumcision sites in newborn infants.

separately because of the uniqueness of this complication. All were clean operations and all were major cases, with the exception of the two circumcisions, both done on newborn infants. Cultures of suppurative material from these two circumcision wounds revealed the presence of coagulase positive *Staphylococcus aureus*. Phage typing showed one circumcision infection to be phage I and 44 A, and the other one 44 A.

Furuncles.—The next most frequent postoperative complication has been furuncles. The fact that furuncles appeared in a postoperative period after the patients had been in the hospital for a few days suggests that the infection was acquired after admission to the hospital. These furuncles were associated with other staphylococcal complications in 4 of the 12 cases. Two patients developing furuncles also developed staphylococcal wound infections. One of the patients with staphylococcal parotitis subsequently developed furuncles. One patient who was treated on a medical ward for 2 months was readmitted to the surgical service one month following discharge. His presenting complaint was intestinal obstruction due to an incarcerated ventral hernia. Furuncles on the skin over the hernia were noted on admission. Exploration and hernia repair was performed on the day of admission and revealed generalized peritonitis. Cultures from the peritoneal exudate, the furuncles, and the subsequent wound infection all revealed a coagulase positive *Staphylococcus aureus* as the organism present. All cultures showed an identical resistance pattern. Peritoneal invasion from the furuncles through the attenuated subcutaneous tissue over the ventral hernia had apparently occurred in this case. This patient probably acquired the staphylococcal infection while hospitalized on the medical service but did not develop the furuncles until after discharge. This patient represents one of the deaths in this series.

Parotitis.—It is of interest to note that 3 cases of parotitis occurred in this group of patients. Acute suppurative parotitis is uncommonly encountered in surgical practice at present. However, Levin[24] reported 3 cases observed during a 3-month outbreak of staphylococcal infections in a New England hospital. Pulaski and Keeling[25] reported 2 cases of postoperative parotitis due to *Staphylococcus aureus.* Such reports indicate that parotitis continues to be a potential hazard in the postoperative period. Of the 3 cases in this series, one required incision and drainage, while the other 2 subsided under appropriate antibiotic therapy.

Bacteremia and Septicemia.—Of the major complications, bacteremia and septicemia due to *Staphylococcus aureus* occurred in 5 instances. Of these 5 patients, 3 recovered and 2 died. In both instances, the death was thought to be due to the staphylococcal septicemia. A mortality rate of 40 per cent is not thought to be excessive for this severe complication. In 4 of these 5 patients, the clinical course was quite typical in that several days following operation the patients developed high spiking temperatures usually in the range of 104° to 106° F., accompanied by chills, leukocytosis, and an acute toxic clinical appearance. Blood cultures were consistently positive for *Staphylococcus aureus,* coagulase positive in 3 cases. Following appropriate antibiotic therapy, 2 cases made an uneventful complete recovery. The fifth case, a 7-year-old child, was admitted with fever and abdominal findings consistent with appendicitis. Laparotomy and removal of a normal appendix was performed the day of admission. Blood cultures taken that evening grew a *Staphylococcus aureus,* coagulase positive, with the phage type and antibiotic resistance pattern of the "hospital" or "endemic" staphylococcus present in this hospital. The exact source of the infection in this patient has not been determined. Neither the patient nor any member of his family had been seen at this hospital in the past. No other member of the family had been ill or treated at another medical facility. Two other patients in this series were transferred to this hospital from other hospitals in this state and had phage 81 staphylococcal infections at the time of admission here.

Meningitis.—Two cases of acute staphylococcal meningitis occurred. One was secondary to a ventriculogram performed on an infant, and the other one was secondary to staphylococcal septicemia occurring during the convalescence from the repair of a cystocele. Complete recovery occurred in both cases.

Osteomyelitis.—The two cases of osteomyelitis occurred in cranial bones following neurosurgical procedures. The brain abscess also occurred following a neurosurgical procedure.

Deaths.—A total of 6 deaths occurred in this series. Three of these have been briefly mentioned. One patient died of peritonitis and 2 of septicemia. The fourth death was in one of the patients with parotitis. Following a gastrojejunostomy, a 70-year-old man developed thrombosis in a branch of the superior mesenteric artery with necrosis of 30 cm. of jejunum. This

death was not thought to be due to *Staphylococcus aureus.* The fifth death was in a 68-year-old man with heart disease, congestive failure, and polycythemia vera, who was transferred to the surgical service for amputation of a gangrenous foot secondary to generalized arteriosclerosis. Postoperatively, this patient developed a pneumonia. Cultures of the sputum grew a mixed flora, including a *Staphylococcus aureus* phage 81. His hospital course was protracted and gradually downhill. Although the death in this poor-risk patient was due to associated medical disease, the staphylococcus infection in the immediate postoperative period contributed to his death. The last death was in an 18-day-old infant with meconium ileus, who was admitted here following a preliminary ileostomy. Suppurative material from the wound infection at the time of admission grew a mixed flora including a phage 81 *Staphylococcus aureus.* Intestinal obstruction required a laparotomy on the second day in this hospital. This death was not thought to be due to *Staphylococcus aureus* but to the primary disease.

DISCUSSION

A breakdown of the complications in this report by years is shown in Table III. Part of the marked increase noted in the period 1957 to 1958 is possibly due to a greater awareness of the problem in the past 2 years with greater efforts being made to search for and culture skin lesions. However, the total number of major complications have shown a definite increase during this period.

TABLE III. DISTRIBUTION BY YEARS OF THE 55 PATIENTS INCLUDED IN STUDY*

	1955	1956	1957	1958 (FIRST 9 MONTHS)
Number of complications	4	8	21	22

*The increase noted during 1957 and the first 9 months of 1958 is obvious.

A truer picture of the current problems in this hospital can be gained by reviewing wound infections. The accuracy of observation and bacteriologic study of wound infections has been constant during the period of this study. The figures are for the general surgical service only, but both charity and private cases are included. The increase in wound infections is statistically significant. Review of the charts in which adequate bacteriologic reports are available show the percentage of wound infections in which a coagulase positive *Staphylococcus aureus* has been cultured, either alone or in combination with other organisms, has approximately doubled in the period 1957 and 1958 compared with the period 1955 and 1956.

TABLE IV. OVER-ALL WOUND INFECTION RATE ON THE GENERAL SURGICAL SERVICE DURING THE YEARS, JAN. 1, 1955, TO OCT. 1, 1958

	1955	1956	1957	1958 (FIRST 9 MONTHS)
Number of operations	1,495	1,397	1,471	952
Number of infections	22	21	39	27
Infection rate (%)	1.5%	1.5%	2.7%	2.8%

Although the postoperative wound infections have shown a significant increase in this hospital in the past 2 years, the over-all infection rate is still lower than others that have been reported. Howe[19] reported an over-all infection rate varying from 1 per cent in 1949 to 4 per cent in 1953. Blowers and his associates[4] reported an increase in wound infection rate from 2 per cent in 1949 to 10.9 per cent during the first 5 months of 1952. Godfrey and Smith[14] made a survey of the patients hospitalized in their hospital in December, 1956, and found 11.1 per cent of the patients had pus-forming staphylococcic infections of some type.

As demonstrated in Table I, wound infections were by far the most frequent postoperative complication. *Staphylococcus aureus* has apparently always been the most frequent organism in infected wounds. Douglas and others,[9] in 1920, reported a study of 61 infected war wounds in which all but 9 were infected with *Staphylococcus aureus.* Ives and Hirshfeld,[21] in a very careful bacteriologic study, emphasized the importance of *Staphylococcus aureus* in wound infections. Since the advent of antibiotics, *Staphylococcus aureus* has continued to be the most frequent organism resulting in postoperative wound sepsis.[8, 18, 19]

Of primary clinical importance in the management of staphylococcal infections is the fact that there has been a steadily increasing incidence of resistant strains of staphylococci.[11, 12, 22] A very complete review of the problem of antibiotic-resistant bacteria has been made by Finland.[13] Finland concluded that the percentage of penicillin-resistant staphylococci isolated from many hospitals in many countries has increased in recent years so that 75 per cent of all strains are now resistant to penicillin. In the present series, 80 per cent of the staphylococci were penicillin-resistant; 72 per cent were also resistant to tetracycline. In the early years of the study (from 1955 through 1956) 80 per cent of the staphylococci isolated were sensitive to erythromycin. In the time period 1957 to 1958, only 55 per cent were sensitive to erythromycin. However, in no instance did the sensitivity pattern change in any patient during treatment. Of the few patients who were treated for many weeks and repeated cultures and sensitivity studies done, there was no incidence of resistance to any antibiotic developing during treatment. This is in accordance with the same findings cited by Finland.[13] It is worthy of note that Chloromycetin was effective in vitro in all instances tested. This reflects the fact that this drug has been infrequently used in recent years in this hospital. Similarly, Albamycin, Spontin, and oleandomycin are effective against these organisms because these drugs have been used for a relatively short period of time. It is anticipated that strains resistant to these antibiotics will emerge in proportion to the degree to which these drugs are used in the future.

PREVENTION AND CONTROL

The fact that staphylococcal infections occurring in hospitalized patients are due to cross infection from other patients and from hospital personnel has

been amply demonstrated.[2, 7, 13, 19] The control of these infections, therefore, must rest on very rigid aseptic techniques in the management of patients in order to break the chain of cross infection. This requires very meticulous attention to strict asepsis during all phases of wound management. In addition to the cross contamination occurring in this hospital, 3 of the patients in this series were admitted with phage 81 infections. Two were transferred from other hospitals but one had no prior known contact with any medical facility. If other phage 81 staphylococcal infections besides postoperative complications are included, there is an increasing number of patients admitted to this hospital for the first time who have phage 81 infections or positive nasal cultures for phage 81 *Staphylococcus aureus.* This observation is based on the fact that one of us (F. J. W.) is Co-director of the Infectious Disease Control Program, and the laboratory reports all positive phage 81 cultures to the infectious disease control officer so that appropriate control measures may be instituted. In view of this fact, it is mandatory that careful screening of all patients admitted to a hospital be accomplished to control cross contamination of other patients and personnel.

Shooter and co-workers[26] reported an outbreak of postoperative infections which they traced to air-borne bacteria being drawn into the operating room by the ventilating system. This was controlled by modifying the ventilating system to reverse the air flow. (We have not had to face this problem as our operating rooms are air-conditioned and recirculated air passes through filters before recirculation into the operating rooms.)

Prophylactic antibiotics are not utilized on the general surgery service. The valid reasons against their use have been well stated.[1, 5, 6, 18, 19] It has never been demonstrated that prophylactic antibiotics are effective in preventing infections. Prophylactic use of antibiotics will hasten the emergence of antibiotic-resistant strains of organisms. We, therefore, feel that antibiotics should be administered only when evidence of an infection exists.

Carriers.—Nasopharyngeal cultures of all personnel working in this hospital have been made in the past. Continuing surveys are made on nursery and operating room personnel. All personnel who have developed a clinical infection are restricted from duty. Nasal carriers are currently being treated with local instillation of antibiotic ointment into the anterior nares.

There is no doubt that nasal and skin carriers among hospital personnel are important.[5, 10, 13, 18, 19] In some instances, outbreaks of infection have been traced to healthy carriers but the importance of healthy carriers in the over-all picture is difficult to evaluate. Burnett and co-workers[6] cultured 649 members of their hospital personnel and found coagulase positive *Staphylococcus aureus* in 41 per cent. Only 4 per cent carried the 80-81 type which was responsible for 60 per cent of their hospital infections. Serial cultures of these carriers showed considerable variation between the presence and absence of positive cultures. (These carriers were not treated with antibiotics.) Barber and Burston[3] expressed the concept that it is doubtful whether

a high carrier rate is the cause or reflection of the hospital infectious process. Their studies showed a high carrier rate in maternity nurses and that organisms of the same phage type were passed to the baby's nose. However, no serious infections occurred until a nurse with an active boil came on duty. Howe[19] noted an increase in staphylococcal infections at a time when his carrier rate was relatively low. Howe feels that the strain and virulence of the organism carried are more important than the number of carriers and that the presence of an active infection in the hospital environment is more dangerous than a high carrier rate.

Treatment.—Once a staphylococcal infection is established in a hospitalized patient, the maximum practical amount of isolation of that patient should be accomplished to prevent contamination of personnel and other patients. In situations where isolation of patients with septic wound proves impractical, Howe[20] recommends local isolation of infected wounds by impermeable occlusive dressings, and of the nasopharynx and skin by masks and gloves.

In The John Sealy Hospital, an Infectious Disease Control Program has been inaugurated. A special hospital unit has been opened and patients with a staphylococcus 80/81 infection are transferred to this unit. In this unit, strict aseptic technique in all phases of patient management is practiced. An outpatient clinic is also operated where continuing personnel carrier surveys are supervised and where all personnel with suspicious skin lesions must be examined before being allowed to continue working. This Infectious Disease Control Program is aimed primarily toward the control of staphylococcal infections but other severe or highly contagious infections are also treated in this unit. This program is a cooperative effort of the various services in the hospital. It is believed that the over-all low wound infection rate (2.8 per cent) is a reflection of this control program.

In the management of staphylococcal infections, adequate surgical incision and drainage are mandatory. Appropriate antibiotics in adequate doses should be immediately instituted. If physicians are familiar with the characteristics and antibiotic resistance patterns of the "hospital" or "endemic" *Staphylococcus aureus* in their own hospital, appropriate antibiotics can be started immediately upon diagnosis of a *Staphylococcus aureus* infection. The delay while sensitivity studies are performed is thus avoided.

SUMMARY AND CONCLUSIONS

All postoperative complications due to *Staphylococcus aureus* from Jan. 1, 1955, to Oct. 1, 1958, at The John Sealy Hospital have been reviewed. Wound infections were the most common complication and furuncles were the second most common. Three cases of parotitis were observed. Other less frequent complications included peritonitis, pneumonia, meningitis, osteomyelitis, peritoneal abscess, and brain abscess.

The majority of these infections, particularly furuncles, are felt to be infections acquired in the hospital by cross-contamination from other patients

and hospital personnel. An increasing number of patients admitted to this hospital for the first time have phage 81 infections or positive nasal cultures for phage 81 *Staphylococcus aureus*. This makes careful screening of patients mandatory.

A significant increase in postoperative complications due to *Staphylococcus aureus* was observed in 1957 and 1958 as compared with 1955 and 1956. Similar experiences have been reported in other hospitals.

Basic principles to be followed in the control of these infections include:

1. Careful aseptic technique in wound management.
2. Isolation of patients with active infections.
3. Prompt, vigorous treatment of established infections.
4. Avoidance of prophylactic antibiotics which hasten the emergence of antibiotic-resistant strains.
5. Careful screening of patients at the time of admission to detect staphylococcal infections or carriers.
6. An adequate carrier control program.

A well-organized infectious disease control program with 100 per cent cooperation on the part of all staff members and hospital personnel is mandatory in order to cope with the staphylococcal problem. It is felt that the low infection rate reported in this review can be accounted for, at least in part, by the rigid control program set up in The John Sealy Hospital.

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METABOLIC ALKALOSIS FOLLOWING MASSIVE TRANSFUSION

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WITH the advent of modern surgical technique, the liberal use of whole blood transfusion has become widespread. It is often assumed that blood transfusion results in a metabolic acidosis in the recipient. Were the patient to be in shock one might also expect a progressive acidosis to arise from the hypoxic condition of the tissues with a lactic and pyruvic acidemia.[9]

Gibson and associates[4] have shown that freshly drawn normal human blood in acid-citrate-dextrose (ACD) solution has a pH of 7.0; this is the result of the acidity of the ACD solution. Because of continued glycolysis and formation of lactic and pyruvic acids by the actively metabolizing red blood cells, the pH may further decrease to about 6.6 after 21 days of storage at 7° C.

If the citrate of infused banked blood were to be metabolized completely, the resulting sodium load, effectively that of sodium bicarbonate, could produce a metabolic alkalosis. Burnett and co-workers[2] have discussed this possibility following massive transfusion in battle casualties. Earlier, Snapper[12] mentioned the value of sodium citrate and alkalization as an aspect of exchange transfusion in the treatment of acute renal failure.

It is the purpose of this paper to report the phenomenon of metabolic alkalosis following multiple closely spaced transfusions.

MATERIALS AND METHODS

Seven consecutive patients, each of whom received over 4,600 ml. of citrated banked blood, were studied. All developed a metabolic alkalosis of varying degrees in the posttransfusion period. None received any alkalinizing therapy other than the sodium citrate present in the ACD solution, representing a minimum of 600 ml. of ACD Solution A.

Serum sodium and potassium concentrations were determined in a Baird flame photometer. Serum chloride concentration was determined using the method of Schales and Schales.[10] Whole blood pH was measured anaerobically on arterial blood at 38° C. in a Cambridge Research Model pH meter calibrated against a known buffer standard, pH 6.975, before and after each determination. Total carbon dioxide content was determined on plasma separated under oil by

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the method of Van Slyke and Neill[13]; partial pressure of carbon dioxide was calculated using the Henderson-Hesselbalch equation with $pK' = 6.10$ and the solubility factor for carbon dioxide = 0.0301 mM/L.

Acid-base data have been charted using the pH:bicarbonate diagram of Davenport.[3]

CASE REPORTS

CASE 1.—H. L. (Hospital No. 9K771), a 45-year-old druggist, was admitted May 22, 1957, because of a 5-year history of intermittent blood-streaked diarrhea which had become more severe during the past month prior to hospital admission. The diagnosis of chronic ulcerative colitis was made. He was begun on intensive medical management including cortisone therapy, but, because of the development of acute abdominal findings with tenderness and persistent distention, he underwent subtotal colectomy 8 weeks following admission. At operation, the colon was necrotic and tore easily. Massive peritoneal contamination required insertion of intraperitoneal drains. Postoperatively the patient developed peritonitis with ileus which responded to antibiotic therapy. Twenty-three days following colectomy he experienced a sudden massive abdominal hemorrhage as evidenced by bleeding from the pelvic drain site. At reoperation he was found to be bleeding from necrotic right colic and middle colic arterial stumps. During and following this massive hemorrhage, the patient received 51 units of citrated whole blood within a 24-hour period.

During transfusion he had a marked metabolic acidosis; blood pH was 7.21, pCO_2 42 mm. Hg, and HCO_3 16.2 mEq./L. Forty-eight hours after transfusion he had a marked metabolic alkalosis; blood pH was 7.53, pCO_2 41 mm. Hg, and HCO_3^- 33 mEq./L. Serum Na^+ concentration was 140 mEq./L., K^+ 3.7 mEq./L., and Cl^- 96 mEq./L.

TABLE I. CASE 1

DATE	pH	$T.CO_2$ (mM./L.)	pCO_2 (mm. Hg)	HCO_3^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	DISTURBANCE
Aug. 19 4:00 A.M.	7.40	22.8	36	21.7	132	3.7		Normal
Aug. 19 9:00 A.M.	7.21	17.5	42	16.2				Metabolic acidosis, marked
Aug. 20	7.40	29.5	48	28.1	140	3.8	94	Metabolic alkalosis with mild respiratory acidosis
Aug. 21 5:00 A.M.	7.45	32.5	45	31.2	140	3.7		Metabolic alkalosis
Aug. 21 8:00 A.M.	7.53	34.2	41	33.0	140	3.7	96	Metabolic alkalosis, marked
Aug. 22	7.47	31.3	43	30.0	141	3.7		Metabolic alkalosis
Aug. 23	7.56	30.4	34	29.4	140	3.7		Metabolic alkalosis with mild respiratory alkalosis
Aug. 25	7.47	31.1	42	29.8				Metabolic alkalosis
Aug. 26					134	2.5		

CASE 2.—S. S. (Hospital No. 5L249), a 42-year-old man, was admitted Aug. 21, 1957, 6 hours after a crushing injury of the abdomen. He had received 6 units of whole blood as treatment for hypotension in another hospital during this time. Physical examination in the emergency ward showed an anxious, robust man, ashen in color. His pulse rate was 130, blood pressure 100/70. The abdomen was slightly distended with generalized direct and rebound tenderness; spasm was most marked in the left lower quadrant. He was transferred to the recovery ward where 12 units of blood were rapidly administered. At exploratory laparotomy 2,000 ml. of fresh, unclotted blood was aspirated from the abdominal cavity. A splenectomy was performed, a tear in the posterior portion of the mesentery was closed, and a bleeding vessel was ligated. He received 5 more units of blood after operation. The citrated whole blood received during his first 24 hours following injury totaled 23 units.

On admission, after having received 6 units of citrated blood and in shock, the patient had a metabolic acidosis; his pH was 7.34, pCO_2 37 mm. Hg, and HCO_3^- 19.2 mEq./L. Thirty-six hours later he had a metabolic alkalosis with a mild respiratory acidosis; blood pH was 7.41, pCO_2 48 mm. Hg, and HCO_3^- 29.3 mEq./L.

TABLE II. CASE 2

DATE	pH	$T.CO_2$ (mM./L.)	pCO_2 (mm. Hg)	HCO_3^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	DISTURBANCE
Aug. 21	7.34	20.3	37	19.2				Metabolic acidosis
Aug. 22	7.40	28.1	45	26.8	143	4.0	103	Normal
Aug. 23	7.41	30.7	48	29.3				Metabolic alkalosis with respiratory acidosis
Aug. 26	7.50	33.2	42	31.9	130	3.2	90	Metabolic alkalosis
Sept. 13	7.46	24.5	34	23.5	139	4.1	82	Respiratory alkalosis, very mild
Sept. 17	7.41	30.0	47	28.6	133	4.1	80	Metabolic alkalosis with mild respiratory acidosis
Sept. 24	7.43	20.7	31	19.8	131	4.1	90	Metabolic acidosis with respiratory compensation
Oct. 22	7.44	25.2	37	24.1	123	3.9	97	Normal

CASE 3.—E. L. (Hospital No. 9D839), a 56-year-old practical nurse, was admitted Oct. 25, 1957, with a chief complaint of hematemesis. She denied digestive symptoms or melena prior to the present episode. During the first 24 hours of hospitalization, hematocrit declined from 37 to 22 per cent, and she developed profound shock. Accordingly, she was given 6 units of citrated whole blood rapidly. Because of three prior hemorrhages and the seriousness of the circumstances, an emergency gastrectomy was carried out in an attempt to control the gastric hemorrhage. Bleeding gastritis was found. Immediately after operation she developed hypotension which responded temporarily to transfusion. Because of recurrence of tachycardia and decrease in the blood pressure necessitating further blood transfusion, she was returned to the operating room where bleeding short gastric vessels were ligated. Her two operations and intervening supportive therapy required 17 units of blood. A total of 23 units of citrated whole blood was administered to this patient within 48 hours. At the end of that time she had a marked metabolic alkalosis; her blood pH was 7.53, pCO_2 42 mm. Hg, and HCO_3^- 33.9 mEq./L. Serum Na^+ concentration was 143 mEq./L., K^+ 3.9 mEq./L., and Cl^- 90 mEq./L.

TABLE III. CASE 3

DATE	pH	$T.CO_2$ (mM./L.)	pCO_2 (mm. Hg)	HCO_3^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	DISTURBANCE
Oct. 27	7.41	24.0	37	22.9				Normal
Oct. 28	7.53	35.2	42	33.9	143	3.9	90	Metabolic alkalosis, marked
Oct. 29	7.50	33.1	42	31.8				Metabolic alkalosis
Oct. 30	7.51	33.1	41	31.9	148	4.3	102	Metabolic alkalosis
Oct. 31	7.46	34.9	48	33.4				Metabolic alkalosis with mild respiratory acidosis
Nov. 4					145	5.6	107	
Nov. 5	7.40	27.3	43	26.0				Normal

CASE 4.—H. B. (Hospital No. 5L642), a 69-year-old carpenter experienced severe lower pelvic pain 4 days prior to admission on Nov. 4, 1957, while hunting birds in the Maine woods. Pain subsided until the day of admission when it recurred and was associated with a syncopal attack. Physical examination on admission revealed a well-nourished man

in mild distress. Pulse rate 80, blood pressure 148/96. A tender pulsatile left lower quadrant abdominal mass was palpated. Hematocrit was 34 per cent. At operation, a large aneurysm of the aortic bifurcation was resected and replaced with a Dacron prosthesis. During the procedure the patient received 8 units of citrated whole blood. Just before operation he was in normal acid-base equilibrium; blood pH was 7.42, pCO_2 41 mm. Hg, and HCO_3^- 26.1 mEq./L. Serum Na^+ concentration was 140 mEq./L., and K^+ 3.6 mEq./L. Eighteen hours after aneurysmectomy a mild metabolic alkalosis had developed; pH was 7.44, pCO_2 44 mm. Hg, and HCO_3^- 28.7 mEq./L. Serum Na^+ concentration was 133 mEq./L., K^+ 3.7 mEq./L., and Cl^- 98 mEq./L.

TABLE IV. CASE 4

DATE	pH	$T.CO_2$ (mM./L.)	pCO_2 (mm. Hg)	HCO_3^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	DISTURBANCE
Nov. 4	7.42	27.3	41	26.1	140	3.6		Normal
Nov. 5	7.44	30.0	44	28.7	133	3.7	98	Metabolic alkalosis
Nov. 6	7.43	29.3	44	28.0	131	4.1	97	Metabolic alkalosis, mild
Nov. 8	7.46	29.0	40	27.8	133	3.0	97	Metabolic alkalosis, mild
Nov. 12	7.48	29.1	39	27.9			99	Metabolic alkalosis
Nov. 20	7.41	29.1	45	27.7	137	4.4		Metabolic alkalosis, mild

CASE 5.—J. M. (Hospital No. 8L280), a 61-year-old man, was run over by an automobile on New Year's Day, 1958, and entered the emergency ward in shock with a compound comminuted fracture of the left leg, fractures of the pelvis and skull, and a rapidly expanding hematoma of the right thigh, hip, and right lower quadrant of the abdomen. An intravenous catheter was inserted and 5 units of blood administered rapidly; following this, blood pressure rose to 108 mm. Hg systolic. Despite continued blood replacement, he showed an unstable blood pressure, rising pulse rate, and rapidly enlarging right lower abdominal hematoma mass. Since he had received 14 units of blood and was still bleeding, the patient was prepared for emergency operation. Arterial bleeding was encountered in the retroperitoneal area, presumably from the superior gluteal artery. This was controlled by ligation of the right hypogastric artery. The wound was closed, the extraperitoneal hematoma site drained, and the compound fracture of the left leg débrided and placed in a cast. No further bleeding occurred postoperatively. He received a total of 22 units of citrated whole blood during the first 48 hours of hospitalization.

On admission after receiving 5 units of citrated whole blood, the patient had a metabolic acidosis with respiratory alkalosis; pH was 7.44, pCO_2 25 mm. HCO_3^- 16.2 mEq./L. Forty-eight hours later he had a metabolic alkalosis; blood pH was 7.47, pCO_2 36 mm. Hg, and HCO_3^- 25.4 mEq./L. Serum Na^+ concentration was 136 mEq./L., K^+ 4.9 mEq./L., and Cl^- 109 mEq./L.

TABLE V. CASE 5

DATE	pH	$T.CO_2$ (mM./L.)	pCO_2 (mm. Hg)	HCO_3^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	DISTURBANCE
Jan. 1	7.44	17.4	25	16.2				Metabolic acidosis with respiratory alkalosis
Jan. 2 1:00 A.M.	7.65	21.6	20	21.0				Respiratory alkalosis
Jan. 2 10:00 A.M.	7.56	22.1	25	21.4	147	6.5	99	Respiratory alkalosis
Jan. 3	7.47	26.5	36	25.4	136	4.9	102	Metabolic alkalosis
Jan. 5	7.56	28.3	32	27.4				Metabolic and respiratory alkalosis
Jan. 7	7.49	27.2	35	26.1				Metabolic alkalosis
Jan. 8					137	3.0	104	
Jan. 14	7.37	24.6	42	23.4				Normal

CASE 6.—J. N. (Hospital No. 4M44), a 59-year-old man, was admitted April 8, 1958, having vomited coffee-ground material and passed tarry stools 4 days previously. He had experienced "indigestion" regularly after meals for 20 years; symptoms had been relieved by baking soda and milk. He denied the use of antacids for at least one month prior to admission. Hematocrit was 16 per cent. During the first 24 hours of hospitalization he received 4 units of blood. On the third hospital day, he passed a tarry stool and developed profound shock. Seven more units of blood were required for resuscitation. Emergency gastrectomy was performed. During the operation and the immediate postoperative period, he received 12 more units of blood or a total of 23 units of citrated whole blood within a 4-day period. On the patient's third hospital day approximately 12 hours after transfusion, he had a metabolic alkalosis; blood pH was 7.52, pCO_2 37 mm. Hg, and HCO_3^- 29.4 mEq./L. Serum Na^+ concentration was 138 mEq./L., K^+ 2.8 mEq./L., and Cl^- 101 mEq./L.

TABLE VI. CASE 6

DATE	pH	$T.CO_2$ (mM./L.)	pCO_2 (mm. Hg)	HCO_3^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	DISTURBANCE
April 11	7.52	30.5	37	29.4	138	2.8	101	Metabolic alkalosis
April 12	7.49	33.1	43	31.8				Metabolic alkalosis
April 16	7.41	27.7	43	26.4	148	3.8	104	Normal
April 21	7.49	28.8	37	27.7	142	3.4	99	Metabolic alkalosis
April 28	7.47	28.8	39	27.6	137	3.5	96	Metabolic alkalosis, mild

CASE 7.—T. T. (Hospital No. 4M210), a 58-year-old man, was admitted April 18, 1958, with a 12-hour history of rightsided abdominal pain. During examination in the emergency ward, he suddenly experienced excruciating right upper quadrant pain, became sweaty and ashen in color, and developed profound shock. His abdomen, which had been flat but tender in the right upper quadrant, became distended. Free flow of blood was obtained on needle aspiration of the peritoneal cavity. A tentative diagnosis of a ruptured hepatic artery aneurysm was confirmed at emergency laparotomy. Since the aneurysm rupture site was peripheral, ligature was carried out with prompt hemostasis. The patient received 12 units of citrated whole blood rapidly during and after operation. This restored blood volume within the first 6 hours of hospitalization and pulse rate and blood pressure stabilized within normal limits. On entry in shock, after receiving 12 units of citrated whole blood, he had a combined metabolic and respiratory acidosis; blood pH was 7.18, pCO_2 55 mm. Hg, and HCO_3^- 19.9 mEq./L. Serum Na^+ concentration was 136 mEq./L., K^+ 4.9 mEq./L., and Cl– 95 mEq./L. Twenty-four hours after transfusion he had a metabolic alkalosis with mild respiratory acidosis; blood pH was 7.44, pCO_2 46 mm. Hg, and HCO_3^- 30.3 mEq./L. Serum Na^+ concentration was 139 mEq./L., K^+ 4.9 mEq./L., and Cl^- 98 mEq./L.

TABLE VII. CASE 7

DATE	pH	$T.CO_2$ (mM./L.)	pCO_2 (mm. Hg)	HCO_3^- (mEq./L.)	Na^+ (mEq./L.)	K^+ (mEq./L.)	Cl^- (mEq./L.)	DISTURBANCE
April 18	7.18	21.6	55	19.9	136	4.9	95	Metabolic and respiratory acidosis
April 19	7.44	31.7	46	30.3	139	4.9	98	Metabolic alkalosis and mild respiratory acidosis
April 21	7.41	31.4	49	29.9	132	4.8	89	Metabolic alkalosis and mild respiratory acidosis
April 29	7.44	31.6	46	30.2				Metabolic alkalosis and mild respiratory acidosis

DISCUSSION

The whole blood anticoagulant and preservative currently in general use in most hospital blood banks is ACD solution. This is available in commercial transfusion containers as N.I.H. Solution A or N.I.H. Solution B. For preservation in Solution A, 75 ml. of preservative solution is used with each 500 ml. of whole blood. Preservation of 500 ml. of whole blood in Solution B requires 125 ml. of solution. The composition of these solutions is shown in Table VIII.

TABLE VIII. COMPOSITION OF ACD SOLUTION

	N.I.H. SOLUTION A		N.I.H. SOLUTION B	
	pH 4.8		pH 5.0	
	75 ml. used per 500 ml. blood		125 ml. used per 500 ml. blood	
	contains:		contains:	
COMPOUND	GM.	MEQ.	GM.	MEQ.
Dextrose	2.45	13.6	1.84	10.2
Citric acid	0.80	---	0.60	---
(anhydrous	0.73	3.8	0.55	2.9)
Sodium citrate	1.65	16.8	1.65	16.8

Blood preserved in either of these solutions had had added to it 33.6 mEq. of sodium citrate per liter. Thus, a 70 Kg. man with a blood volume of 5,000 ml. receiving a transfusion involving complete blood volume exchange would receive about 168 mEq. of sodium citrate. This amount of sodium ion (with disposable anion) is contained in one liter of 0.167 M. sodium lactate, 7 L. of Ringer's lactate, or 3.8 ampules of sodium bicarbonate solution containing 44 mEq. of sodium per ampule. If total blood volume exchange takes place several times, as may occur when bleeding is not initially controlled (Case 1), then the citrate ion may have time to equilibrate into the interstitial as well as into the intravascular compartment resulting in even a larger extracellular fluid citrate load. In conditions under which the dynamic relations between bleeding and replacement rates are such as to give the infused sodium citrate a longer average time in the body, even a larger proportion will equilibrate into the interstitial fluid.

In some patients exchange transfusion does not occur. Total blood volume infusion may still be necessary. This is illustrated by the patient with traumatic edema and massive hemorrhage into tissues about a fracture with local pooling of a large amount of blood (Case 5).

Immediately after infusion of banked blood, a metabolic acidosis is usually present and at times may be quite severe depending on the metabolic status of the infused red cells. In addition the degree of acidosis seen in shock depends on the depth and duration of the low perfusion state. In acute hypovolemic shock in man whole blood pH rarely falls below 7.0 but is often seen in the range of 7.15 to 7.25.[11] This results from the accumulation of endogenously produced anaerobic metabolites, chiefly lactic and pyruvic acids. As these are later burned in recovery, blood pH rises and returns to normal. When to this setting is added a large amount of sodium citrate, alkalosis

may result. Because of renal compensation with facultative sodium excretion, the *normal* individual can easily handle an amount of sodium bicarbonate equivalent to the sodium citrate load involved in multiple transfusions without developing an addition alkalosis; however, this mechanism is not manifest

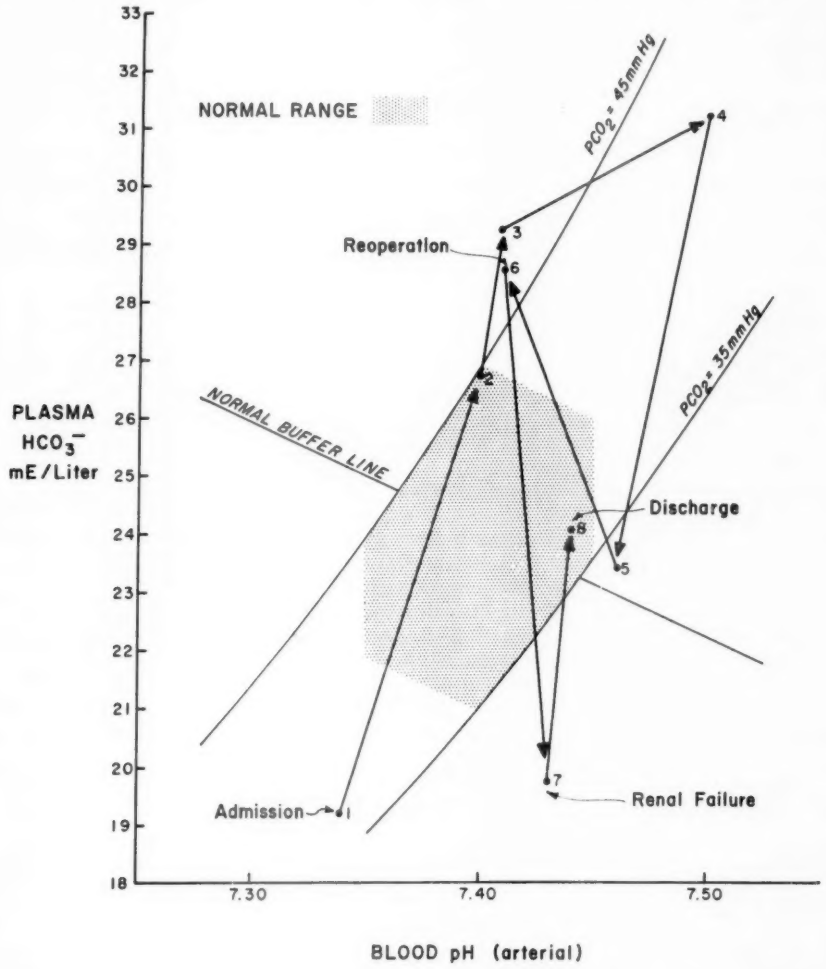

Fig. 1.—In this figure the sequential changes in the pH profile of S. S. (Case 2) are shown. The plot is based on the standard pH-bicarbonate diagram. Points above the buffer line indicate metabolic alkalosis, those below metabolic acidosis. Points to the left of the "pCO_2 45 mm. Hg" line indicate respiratory acidosis; those to the right of the "pCO_2 35 mm. Hg" line indicate respiratory alkalosis. The shaded area encloses the normal range.

On admission (*1*) after having received several blood transfusions rapidly and in shock, a moderate metabolic acidosis was present. As citrate was metabolized (*2,3,4*) a progressive metabolic alkalosis supervened. Later as plasma bicarbonate concentration re-approached the normal range (*5*) reoperation and retransfusion were necessary. This caused an additional mild alkalosis (*6*). After an episode of acute renal failure associated with a severe metabolic acidosis with respiratory compensation (*7*), plasma acid-base findings again returned to normal.

in conditions of stress. The tendency to retain sodium and to reabsorb bicarbonate from the glomerular filtrate so characteristic of the posttraumatic state acts synergistically with sodium citrate to produce a metabolic alkalosis. This is graphically illustrated in Fig. 1 (Case 2).

Sodium citrate is not the only known alkalinizing sodium salt. Any sodium compound containing an organic anion that can be metabolized may be regarded

as potentially alkalinizing. These include such compounds as sodium lactate,[5] sodium glutamate,[14] sodium pyruvate,[7] and sodium acetate.[8]

Undoubtedly, the status of the liver cells at the time of administration will have much to do with the rate of disappearance of citrate from the blood stream.[1] A severely diseased or hypoxic liver with few functional cells will metabolize citrate at a slower rate than normal. This leads to a dangerous accumulation of citrate, and results in chelation of calcium ion. Abnormal myocardial irritability, ventricular fibrillation, and/or tetany may result.*[6] It is our conviction that frank citrate intoxication due to the accumulation of a large excess of unoxidized citrate in the body is a most unusual and exceptional circumstance. When it does occur, it results, usually, from massive citrate transfusion to patients in deep shock, or to patients who have liver disease preventing the oxidation of citrate.

It will be noted that posttransfusion alkalosis represents, in a sense, the reverse of citrate intoxication; it is a result of the metabolic utilization of citrate. Thus the alkalosis produced would be expected to have effects just the reverse of those of citrate on myocardial irritability, i.e., those of hypocalcemia, acidosis, and hyperkalemia.

Minor degrees of citrate accumulation may be significant under special circumstances, quite aside from the massive accumulation usually associated with "citrate toxicity." For example, in a patient with congestive heart failure who is digitalized and who, after an operation, has a moderately high serum potassium concentration, a small load of citrate (by binding calcium ion), may drastically diminish the cardiac effect of digitalis, potentiate the effect of potassium, and result in a marked degeneration of myocardial function. Such effects would be difficult to diagnose by laboratory tests but would be evident if a patient, on digitalis, were to show a marked reduction in myocardial efficiency postoperatively and posttransfusion.

This metabolic alkalosis is probably an effect to be desired. In the ill postoperative patient or in the patient transfused after a severe hemorrhage, alkalinizing therapy may aid in counteracting the metabolic acidosis that results from inadequate tissue perfusion. Although evidence is not conclusive, there are data to suggest that, both in animals and man in the presence of hypovolemia, oliguria, hypotension, and shock, vascular homeostasis and recovery are more easily achieved in a normal or alkaline acid-base setting than in severe acidosis.[11] We believe that the alkalosis of transfusion is an unintentional but probably beneficial by-product of modern blood bank practice. Where pyloric obstruction coexists or there are other sources of alkalosis or hypokalemia, this transfusion alkalosis may be of more dangerous significance.

CONCLUSION

After massive transfusion with whole blood preserved in ACD solution, there is usually an immediate posttransfusion metabolic acidosis due to the low

*The standard ACD solution contains about 30 per cent more citrate than that needed to bind the ionized calcium in the stored blood.

pH of banked blood and poor tissue perfusion. The initial acidosis is followed in several hours by the gradual onset of a metabolic alkalosis most marked on about the third posttransfusion day. This alkalosis is due to the metabolic breakdown of sodium citrate which is used as an anticoagulant in ACD solution.

From these studies it would appear that the minimum amount of sodium citrate necessary to produce a mild alkalosis after transfusion in hemorrhage is about 135 mEq. This would be contained in 8 units of whole blood preserved in 600 ml. ACD Solution A, or 1,000 ml. of Solution B.

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CANNULATION OF THE HUMAN THORACIC LYMPH DUCT

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THE thoracic duct is the principal channel through which lymph collected by major tributaries from the head, neck, thorax, abdomen, and extremities is discharged into the venous system. Cannulation of the thoracic duct in animals is a common procedure for the procurement and study of lymph modified by varying experimental conditions. Human lymph is rarely available for study except when obtained from the occasional patient with chylothorax, chylous ascites, or lymph fistula.[1, 2] Elective cannulation of the thoracic duct can be applied to human subjects for clinical investigation of disease processes involving the lymphatic system.

ANATOMY OF THORACIC DUCT IN NECK

The termination of the thoracic duct was examined in 30 dissections of the neck in cadavers. The duct emerged from the left superior aperture of the thorax and entered into the vertebral triangle (Waldeyer's triangle) at the base of the neck. It ascended over the longus colli muscle up to the level of the sixth or seventh cervical vertebra, arched mediad for a distance of 1 inch and then descended on the scalenus anticus muscle anterior to the phrenic nerve. The cervical section of the thoracic duct resembled in form an inverted "U" and averaged 5 to 12 mm. in width. The jugular lymph trunk, the subclavian lymph trunk, and other collecting lymph tributaries either singly or combined emptied into the thoracic duct before the termination of the latter. The junction of the thoracic duct with the venous system was variable but confined to a relatively limited area. These junctional points were as follows: with the terminal internal jugular vein (18 cases, 63 per cent), with the subclavian vein (7 cases, 22 per cent), with the angulus venosus (3 cases, 10 per cent), and with the innominate vein (2 cases, 6 per cent). Reduplication or double thoracic duct was found in 4 dissections; of these the doubling originated once in the thorax and the other three times in the neck from the ascending limb. In 2 of the latter specimens, the paired ducts joined individually with the terminal jugular vein. In the third specimen the twin ducts drained separately into the jugular vein and subclavian vein while in the fourth specimen they re-formed into a single duct and emptied into the subclavian vein. Other aberrations, such as the paired duct with individual bilateral junctions or the single duct terminating in the veins of the right side of the neck were not observed.[3]

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SURGICAL TECHNIQUE FOR CANNULATION OF THORACIC DUCT

Surgical exposure of the thoracic duct in the neck is not difficult. The oral administration of 2 ounces of heavy sweet cream 1 to 3 hours before operation insures easy identification of the lymphatics. The usual preanesthetic medication is given and the operation may be performed under general or local anesthesia. The patient is placed in the supine position with the neck extended by a sandbag under the shoulder and the face turned to the right. A transverse incision is made at the base of the neck about 1 inch above the clavicle extending from the midline to a point about 1 inch beyond the lateral border of the sternomastoid muscle. The platysma and cervical fascia are opened transversely. The wound is forcibly retracted in an up and down direction and held apart with self-retaining retractors. The medial border of the sternomastoid muscle is mobilized and retracted laterally. The anterior segment of the omohyoid muscle is retracted cephalad. The internal jugular vein is encompassed by a narrow umbilical tape by which it is rotated and retracted medially, exposing to view the angulus venosus and the posterior lateral aspect of its termination into the subclavian vein. The terminal segment of the thoracic duct is exposed by blunt dissection of the subjacent areolar tissue in close proximity to the jugular-subclavian junction. The phrenic nerve is isolated and protected from injury during this dissection.

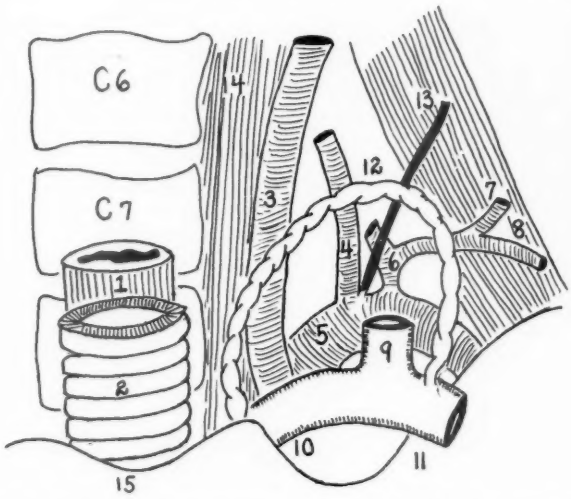

Fig. 1.—Diagrammatic drawing of anatomic structures in the region of the termination of the thoracic duct in the neck.

1, Esophagus. *2*, Trachea. *3*, Common carotid artery. *4*, Vertebral artery. *5*, Subclavian artery. *6*, Thyrocervical trunk. *7*, Transverse cervical artery. *8*, Transverse scapular artery. *9*, Internal jugular vein. *10*, Innominate vein. *11*, Subclavian vein. *12*, Thoracic duct. *13*, Phrenic nerve and anterior scalene muscle. *14*, Longus colli muscle. *15*, Sternum.

Small blood vessels interfering with the isolation of the thoracic duct may be ligated and cut. If the duct is not located in this region the exploration is directed along the medial aspect of the termination of the internal jugular vein and extended along the line of the innominate and subclavian veins. When located the duct is carefully freed from the fatty areolar tissue up to its arch and held by two encircling untied ligatures of No. 3-0 plain catgut. A

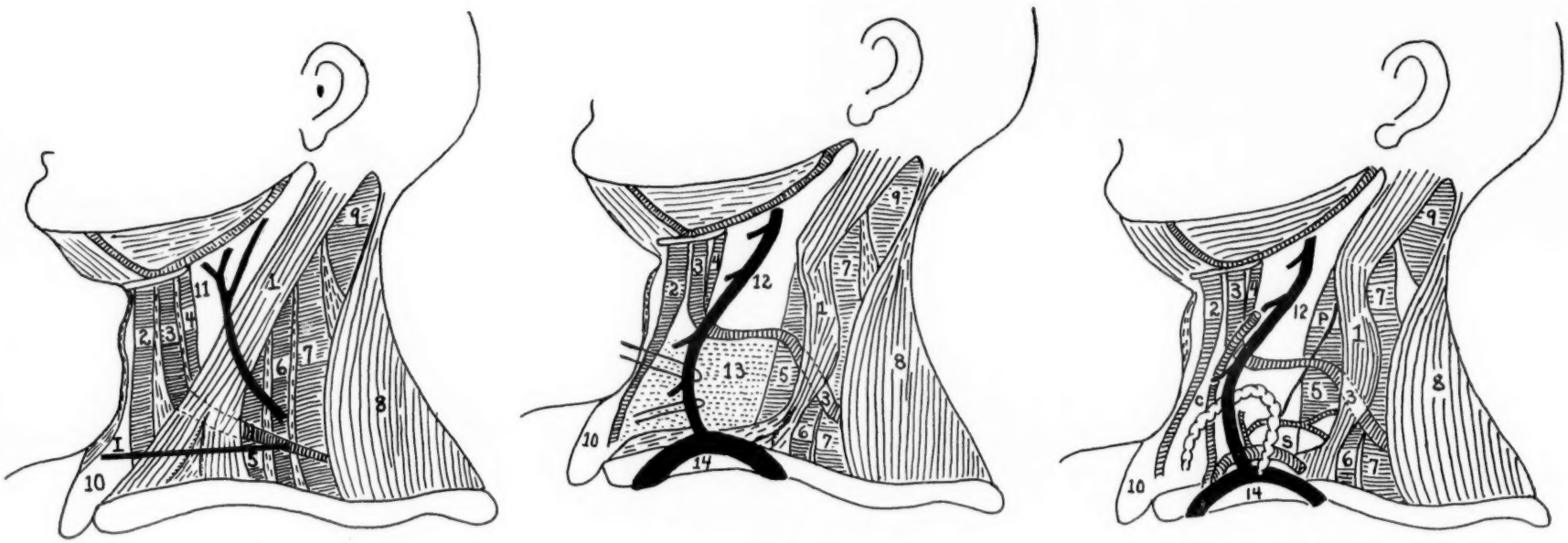

Fig. 2.—Technique for exposure of thoracic lymph duct in neck.

A, Surgical transverse incision at base of neck extending through skin, platysma, and cervical fascia revealing the structures underneath. *B*, Exposure of internal jugular vein and subclavian vein at the junction of the two vessels. The fibroareolar roof of the vertebral triangle is in view. *C*, The thoracic duct is exposed and mobilized at its termination.

1, Sternomastoid muscle. *2*, Sternohyoid muscle. *3*, Omohyoid muscle. *4*, Thyrohyoid muscle. *5*, Anterior scalene muscle. *6*, Middle scalene muscle. *7*, Levator scapulae muscle. *8*, Trapezius muscle. *9*, Splenius capitis muscle. *10*, Suprasternal fossa. *11*, External jugular vein. *12*, Internal jugular vein. *13*, Vertebral space. *14*, Subclavian and innominate veins. *C*, Carotid artery. *P*, Phrenic nerve. *S*, Subclavian artery.

small cut is made in the wall of the duct with fine plastic scissors, the opening is dilated with a mosquito clamp and through it is inserted a No. PE 190/S 12 inch polyethylene catheter. If preferred, the duct may be pierced by a blunt-pointed needle of proper caliber through which the tubing is passed into the lumen. The catheter is advanced into the duct for a distance of about 1½ inches and the two encircling ligatures are tied firmly over it at the point of entrance. The retractors are removed, the muscles are reposited, and the wound is closed with the plastic catheter emerging from the lateral aspect of the incision. Lymph is collected in a bottle at the bedside or if the patient is to be ambulatory it is collected in a test tube fixed to the chest wall with adhesive tape. Clots in the catheter may be removed with a long thin wire and the lymph may be rendered less coagulable by filling the catheter with a dilute heparin solution.

Fig. 3.—X-ray visualization of thoracic lymph duct by retrograde injection of contrast medium through cannula.

EXTERNAL DRAINAGE OF THORACIC DUCT LYMPH

The thoracic duct was cannulated in 22 patients subjected primarily to prescalene lymph node biopsy for cervical adenopathy of varied etiology. Lymph was collected intermittently for periods of 1 to 8 days. Thoracic duct pressure usually taken at the height of maximum flow varied from 10 cm.

to 28 cm. H_2O. The flow of lymph ranged from 14 to 110 ml. per hour and was affected by fluid intake, by intravenous infusions of nutriments, by diet, and by ambulation or exercise. Quantitative biochemical determinations were made of samples of lymph obtained during the postabsorptive state and after meals. These results are recorded in Table I. The concentrations of the constituents in lymph were lower than their counterpart in serum but occasionally the values for the former exceeded those in the blood. Analysis of lymph samples obtained after meals at the height of digestion frequently showed elevations in amylase, lipase, and alkaline phosphatase greater than the values for these enzymes in corresponding samples of blood. In 6 patients the concentration of globulin in the lymph exceeded that of albumin while in the blood the albumin/globulin ratio was normal. The coagulation time of the lymph was markedly variable and usually longer than the clotting time of blood. The white cell count ranged between 400 and 6,800 cells per cubic millimeter with almost a complete predominance of mononuclear lymphocytes.

TABLE I. QUANTITATIVE BIOCHEMICAL DETERMINATIONS OF THORACIC DUCT LYMPH OBTAINED DURING THE POSTABSORPTIVE AND POSTPRANDIAL STATES

Specific gravity	1.012-1.025
Total protein	2.20-5.98 Gm. %
Albumin	1.20-4.16 Gm. %
Globulin	1.10-3.08 Gm. %
Sugar	48-200 mg. %
Urea nitrogen	8-17.6 mg. %
Nonprotein nitrogen	6-14.2 mg. %
Total cholesterol	65-220 mg. %
Cholesterol esters	25-182 mg. %
Inorganic phosphorus	0.8-4.2 mg. %
Fibrinogen	.16-.24 mg. %
Total fat	0.8-4.6 Gm. %
Sodium	104-148 mEq./L.
Potassium	3.8-5.0 mEq./L.
Chloride	85-130 mEq./L.
Calcium	3.4-6.0 mEq./L.
Alkaline phosphatase (Bodansky)	2.0-4.8 u./ml.
Acid phosphatase	0.3-0.8 u./ml.
Glutamic oxalacetic transaminase	22-40 u./ml.
Serum glutamic pyruvic transaminase	5-21 u./ml.
Lactic acid dehydrogenase	150-380 u./ml.
Aldolase	8-20 u./ml.
Amylase	50-83 u./ml.
Lipase	0.5-2.4 ml./.05N-NaOH

The color of lymph varied; it was usually clear in the postabsorptive state, white or cream-colored up to 6 hours after a fatty meal, and occasionally pink in color. Red cell counts made on the latter lymph showed variations in the number of erythrocytes from 200 to 600 per cubic millimeter. The red cell count of clear lymph rarely exceeded 50 cells per cubic millimeter. Discoloration of lymph may be caused by the reflux of blood into the thoracic duct from the junctional vein or may be due to the forced permeation of red cells into lymph capillaries by alteration of pressure gradients in tissue.

The intermittent drainage of lymph externally seemed to be well tolerated, especially because there were no restrictions on the intake of fluids and food.

Two patients with a loss of lymph exceeding 5,500 ml. in 3 days complained of headache, drowiness, moderate thirst, and lassitude. These symptoms ceased when external lymph drainage was stopped and adjustments in increased food intake were made. In one case, a liter of heparinized lymph was returned to the donor intravenously without any untoward reaction except for a mild temperature elevation.

The indwelling plastic catheters yielded easily when pulled and were removed without opening the wound. A pressure dressing was applied to the base of the neck for 48 hours after which the wound usually closed. In 4 patients the discharge of lymph from the catheter sinus persisted for a few days and then closed.

SUMMARY

1. The anatomy of the termination of the thoracic duct in the neck was reviewed and a technique for its cannulation was described.

2. Lymph from the thoracic duct of 22 human subjects was drained intermittently during the absorptive and nonabsorptive states. Biochemical examinations of the fluid were made.

Cannulation of the thoracic duct is a useful technique essential to studies on the lymphatic system. By this method, lymph is available in sufficient quantity for a variety of biochemical and enzyme determinations. In this laboratory, the circulation of malignant cells in the lymph of carcinoma patients is under investigation at present. As in angiography, the injection of a contrast dye makes possible the x-ray visualization of the thoracic duct for localization of obstruction or laceration of this vessel. Catheterization of the thoracic duct is as practical and as safe a procedure as those used in cardiologic studies and entails about the same amount of risk.

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INJECTION STUDIES ON THE MESENTERIC ARTERIAL CIRCULATION

I. Technique and Observations on Collaterals

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IN THE following we present a technique for the postmortem study of the vasculature of the abdominal viscera. The technique is based upon injection of the arteries with radiopaque mass, x-ray angiography, and dissection. In order to reduce the immense overlap of vessel shadows cast upon the x-ray film by the intact visceral aggregate, the abdominal viscera were partitioned so as to simplify the vascular interrelations without impairing radiographic or anatomic examination. General observations on the collateral potential of the normal mesenteric circulation are recorded to serve as an introduction to subsequent reports derived from an extended inquiry into the vascular pathology of the abdominal viscera.

TECHNIQUE

Removal of the Specimen.—The contents of the abdominal cavity including the diaphragm above and the pelvic viscera below are severed en bloc (Rokitansky method) from their retroperitoneal attachments. Care is taken to excise the diaphragm as close to its skeletal attachments as possible.

Preparation of Specimen for Injection.—With the posterior aspect of the specimen facing the operator, the aorta is opened lengthwise. Glass cannulae with flanged tips are inserted into the ostia of the celiac and superior and inferior mesenteric (the "constituent") arteries and secured with strong silk ties.

In order to free the vasculature of postmortem clot and air, each of the "constituent" arteries is flushed with 10 to 20 ml. of saline by a hand-operated syringe. This saline flush also serves to identify (and secure) major vessel leaks especially at the resection edges of the diaphragmatic leaves, at the diaphragmatic inlet of the esophagus, and rectum.

Injection.—The injection mass used consists of a gelatin base which is treated so as to remain liquid at room temperature and which is rendered radiopaque by barium sulfate. Just prior to injection, formalin is added in a

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concentration which will cause the mass to solidify inside the arteries within a predetermined period of time, usually one hour. The mass fills vessels down to a diameter of 40 micra quite regularly. Smaller ones are filled only spottily. The mass does not cross the capillaries. For details of preparation and apparatus the reader is referred to a previous publication.[8]

Individual feeding bottles for the three "constituent" arteries, each filled with about 100 c.c. of injection mass, are connected with the respective cannulae and the whole system is attached to a pressure source. Injection is begun at 50 mm. Hg and raised stepwise to 200 mm. Hg, taking care at all times to secure any leaks not previously identified. We have standardized the injection time at 15 minutes and 200 mm. Hg or until there is no further fall in the level of injection mass in the feeding bottles, whichever comes first. The tubing of the cannulae is then clamped and the apparatus is disconnected. In order to reduce postmortem degeneration of the tissues as well as offensive odors, generous quantities of 1 per cent saline solution of $HgCl_2$ are injected into the lumen of the gastrointestinal tract through multiple punctures, using syringe and needle. The specimen is returned to the icebox where solidification of the injection mass is allowed to take place.

Partitioning of the Specimen.—As soon as the mass has solidified, the specimen is ready for partitioning. It is placed on the table in its natural position, that is, with the intraperitoneal viscera facing the operator and with the topographic relations reconstituted.

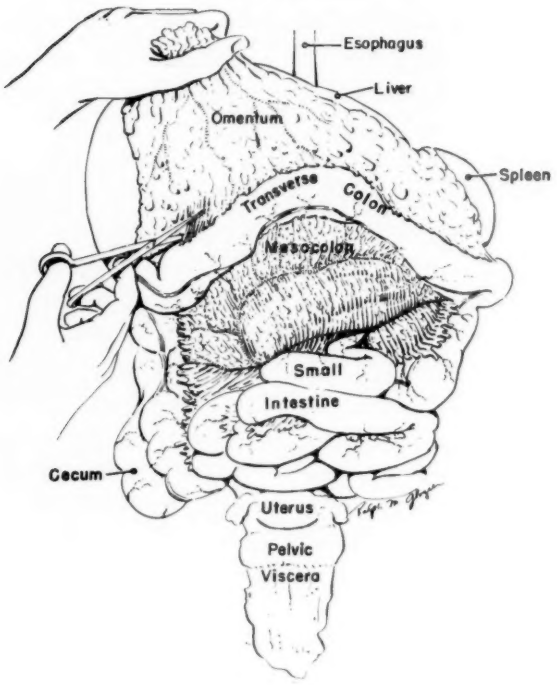
Step I: The omentum is reflected upward and its posterior leaf is dissected off the transverse colon. This opens the lesser omental cavity (Figs. 1 and 2).

Step II: The transverse colon is maximally stretched upward so as to show the whole length and width of the transverse mesocolon. The proximal loops of the small intestine are swept aside uncovering the root of the mesentery of the small intestine. The superior mesenteric artery which may be identified by palpation at its emergence from beneath the pancreas is exposed through a window in the covering mesenteric fat, big enough to visualize also the roots of the middle colic and proximal jejunal arteries (Fig. 3).

Step III: The first loop of the jejunum is closed with dual ligatures as is the mid-transverse colon (Fig. 3). The respective mesenteries are then divided with scissors along the dotted line indicated in Fig. 3. This cut severs the following arteries: the first jejunal arcade, at its zenith; the superior mesenteric artery, between its first and second jejunal branches; and the middle colic artery in its mid-course. In practice, it is, perhaps, more convenient first to divide the superior mesenteric artery and, with this division as the hub, to carry one incision toward the small intestine and the other toward the mid-transverse colon, each cut terminating between the dual ligatures previously tied around the respective segments of intestine.

Step IV: This step is concerned with the isolation of the intestinal tract, from the first loop of the jejunum to the mid-transverse colon. The small intestine is swept over to the right and its mesentery is peeled off by blunt dissection from the (retroperitoneal) duodenum, working from left to right (Fig. 4).

Fig. 1.



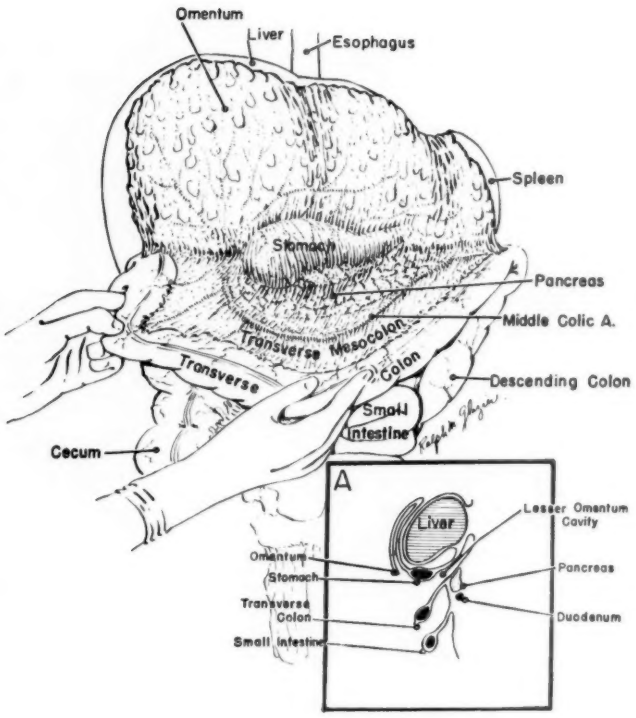


Fig. 2.

Fig. 1.—The greater omentum has been reflected upward. Its posterior leaf is being freed from the transverse colon.

Fig. 2.—Upon completion of Step I, the lesser omental cavity has been exposed. Inset *A* is a diagrammatic sideview of Step I.

Once the duodenum is laid bare, the residual attachments of the mesentery of the small intestine are being freed in continuity with those of the ascending and (proximal) mid-transverse mesocolon (Fig. 4). The specimen thus isolated represents the arborization of the superior mesenteric artery with the exception of its most proximal (retropancreatic) segment.

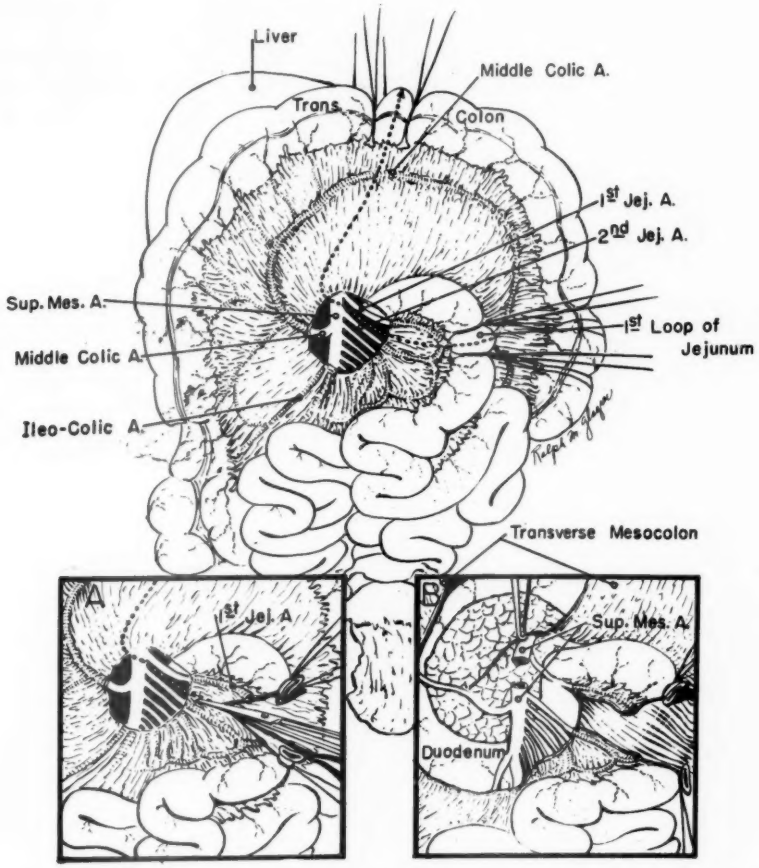


Fig. 3.—A window has been cut into the mesentery of the small intestine so as to expose the superior mesenteric artery at its emergence from behind the pancreas. A cut is made along the dotted line so as to divide, respectively, the first loop of the jejunum and the mid-transverse colon between double ligatures placed to prevent fecal spillage. The cut divides the main stem of the superior mesenteric artery between the first and second jejunal arteries (Insets *A* and *B*).

Step V: This step is designed to liberate the remainder of the colon. The aorta is divided just above the ostium of the inferior mesenteric artery which, without turning the specimen, is identified by palpating the cannula inserted therein. The incision is carried upward and to the left through the posterior parietal peritoneum and the left mesocolic fold making contact with the root of the distal transverse mesocolon (Fig. 5). This is followed by blunt dissection of the distal transverse and descending mesocolons from the perirenal fat. Once the inferior pole of the left kidney has been reached (Fig. 5, *A*), the remainder of the descending colon, the sigmoid, and rectum together with the attached pelvic viscera fall free. The specimen obtained represents the arborization of the inferior mesenteric artery.

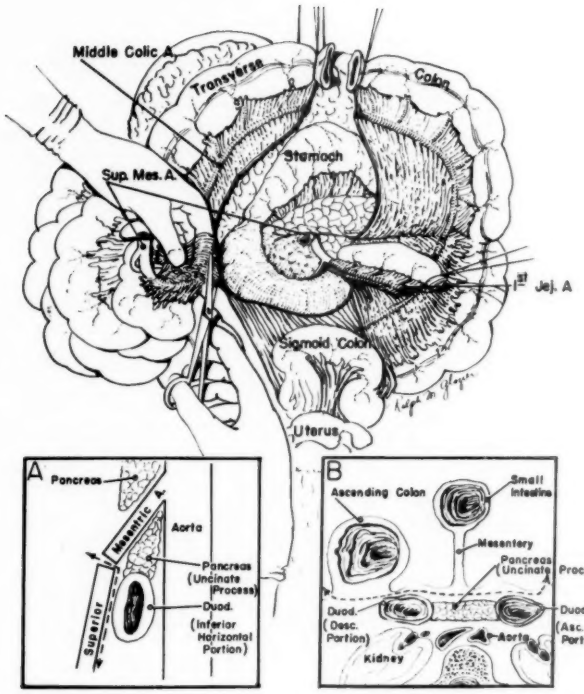


Fig. 4.

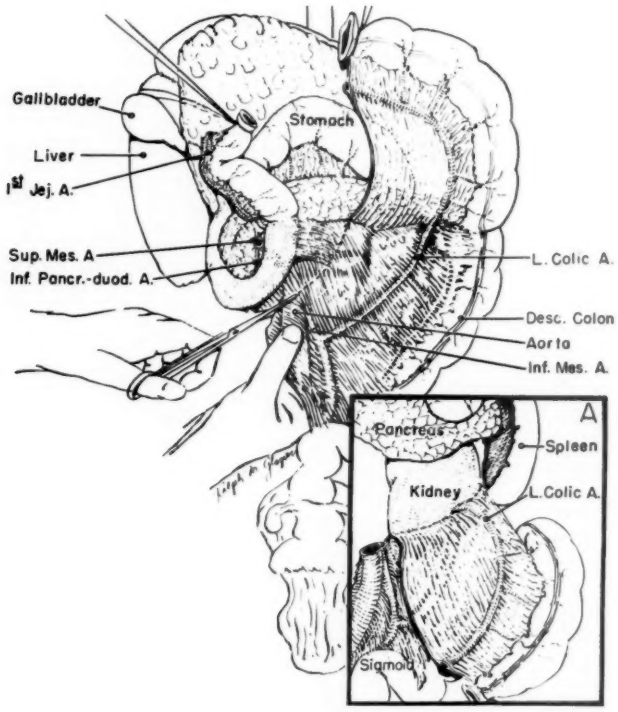


Fig. 5.

Fig. 4.—Isolation of superior mesenteric artery specimen. The entire small intestine with the exception of the proximal segment of the first jejunal loop is being freed by peeling the mesentery off its attachment to the duodenum. (The attachment of the mesentery of the small intestine to the posterior abdominal wall has already been liberated upon removal of the specimen from the body.) The insets *A* and *B* offer a diagrammatic representation of Steps III and IV, respectively.

Fig. 5.—Isolation of inferior mesenteric artery specimen. A cut made across the aorta above the ostium of the inferior mesenteric artery is continued to the root of the remaining transverse mesocolon along the dotted line. The colon is then peeled from its retroperitoneal attachments from above downward (Inset *A*).

With the superior and inferior mesenteric artery specimens partitioned, there remains a third specimen which comprises stomach, duodenum, proximal half of the first jejunal loop, liver, spleen, pancreas, diaphragm, and the (extramesenteric) kidneys and adrenals. This specimen represents essentially, the celiac arborization but contains also the (retropancreatic) root of the superior mesenteric artery.

In summary, the three specimens obtained correspond, respectively, to the distributions of the celiac, superior mesenteric, and inferior mesenteric arteries. Only three sizable arteries required division (Step III): the main stem of the superior mesenteric, the first jejunal arcade, and the middle colic.

Angiography.—Working on a thin Vinylite plate, each specimen is positioned for angiography such as to minimize vascular overlap on the x-ray film. In regard to the superior and inferior mesenteric arborizations, the purpose is accomplished merely by restituting the natural topography of the viscera (Figs. 6 and 7). By contrast, positioning for angiography of the celiac arborization is more complex. It calls, first, for resection of kidneys, adrenals, liver, and spleen, followed by transverse division of the aorta between the ostia of the celiac and superior mesenteric arteries. The complex vasculature about the duodenum and the head of the pancreas is then simplified by converting the natural right convex and downward curve of the duodenum to a right convex and upward curve. This is accomplished by rotating the head of the pancreas by 180 degrees about its long axis such that the second, third, and fourth portions of the duodenum as well as the uncinate process of the pancreas come to present themselves with their posterior surfaces anteriorly. A stereoscopic arteriogram is now being taken (Fig. 8 *A*). This is repeated after the specimen has been further simplified by ablation of the diaphragm, esophagus, and corpus ventriculi (Fig. 8 *B*).

Separate roentgenograms of liver and spleen are also taken.

We have been using nonscreen film mounted either in cardboard folders or paper wrappings (Gevaert Osray x-ray film, individually wrapped) on which is placed the Vinylite plate with the positioned specimen.

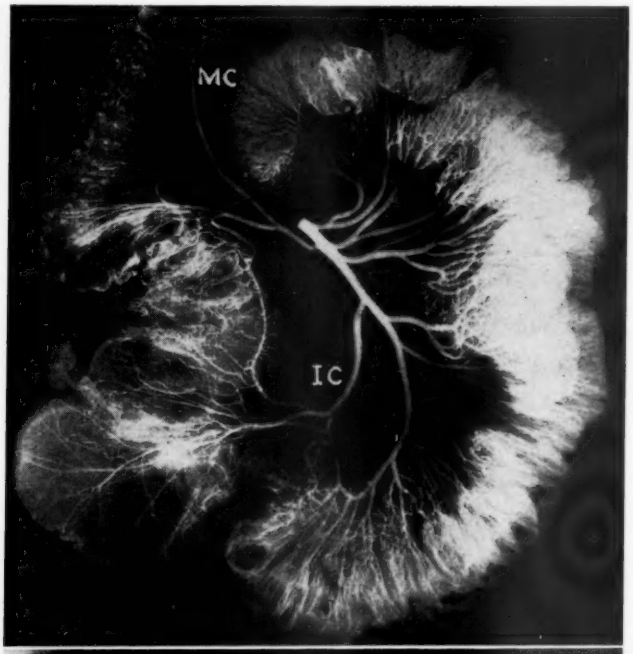
Dissection of the arteries with scissors is begun as soon as the x-ray films are dry. A permanent dissection record of plaques, narrowings, and so forth, is made on tracing paper placed over the illuminated film.

Technical Hints.—In order to identify important anatomic landmarks on the x-ray films, short pieces of thin, flexible copper wire (No. 20) are threaded beneath the serosa and tied into knots at such sites as the pylorus, the duodenojejunal flexure, the ileocecal valve, and the hepatic and splenic flexures of the colon. Accessory and atypical arteries which require division during partitioning may be kept identifiable by tagging their respective cut ends with paired wire ties matched respectively by number of loops, length and configuration of each arm, and the like.

OBSERVATIONS

Collateral Circulation.—The vascular arcade so characteristic of the intestinal tract was recognized in modified fashion also in relation to the stomach

Fig. 6.



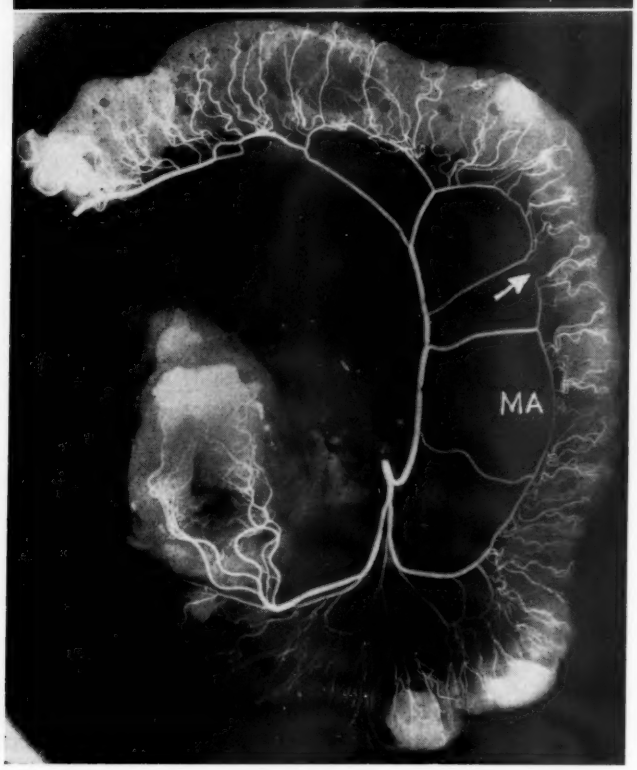
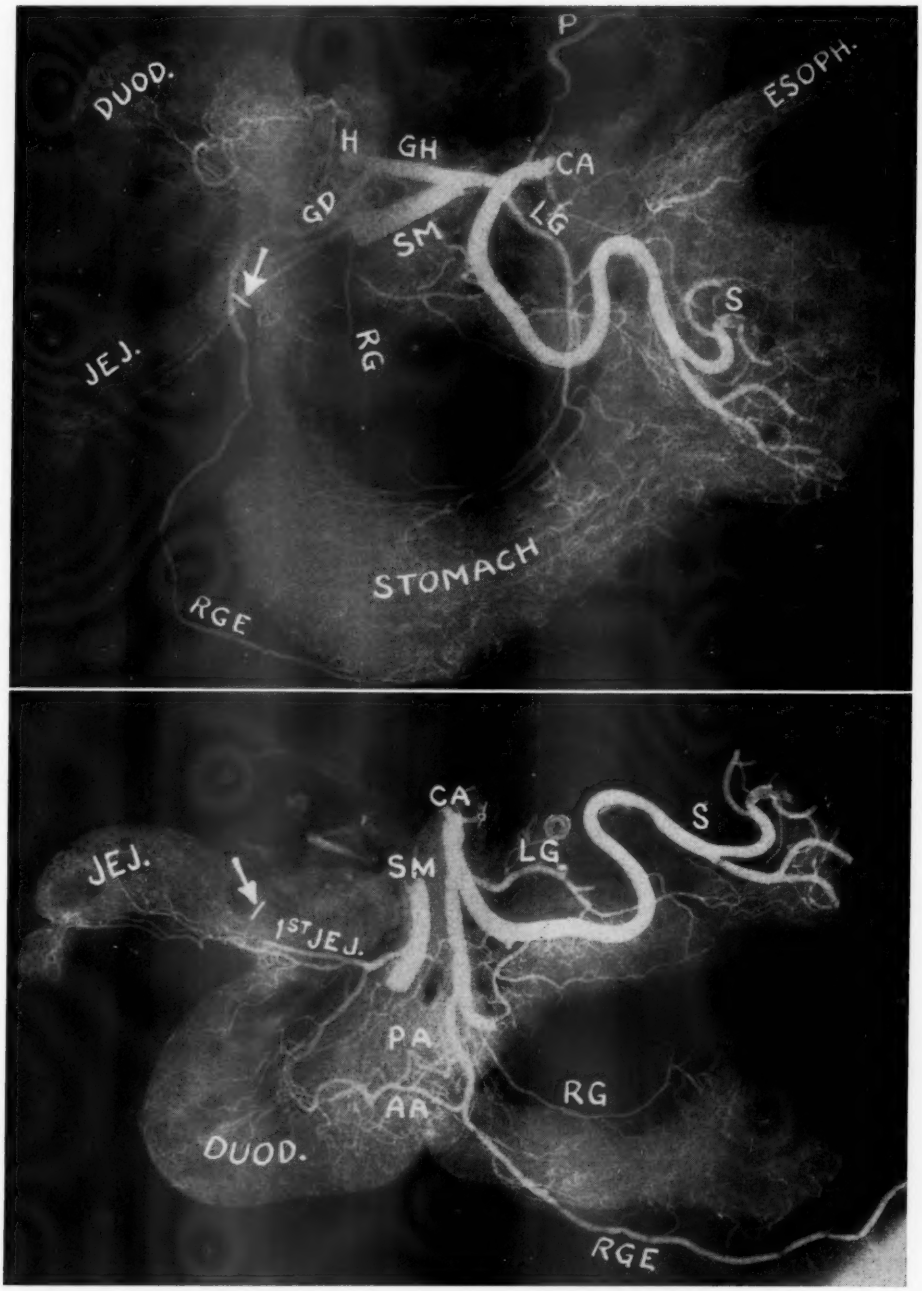


Fig. 7.

Fig. 6.—Superior mesenteric arborization. Only two arteries are given off to the colon, the ileocolic (*IC*) and the middle colic (*MC*). In the majority of specimens there is no right colic artery.

Fig. 7.—Inferior mesenteric arborization. The marginal arcade (*MA*) (so-called Drummond's artery) is incomplete (*arrow*). The splenic flexure is identified by a wire loop.

A.



B.

Fig. 8.—*A*, (A 57-92) Celiac artery specimen with the duodenum in its natural position. Note the undecipherable complexity of the vasculature about the head of the pancreas. Arteries: *CA*, celiac; *GD*, gastroduodenal; *GH* gastrohepatic; *H*, hepatic; *LG*, left gastric; *P*, phrenic; *RG*, right gastric; *RGE*, right gastroepiploic; *S*, splenic; *SM*, superior mesenteric. Because of overlap the superior mesenteric seems to arise from the gastrohepatic artery. The left gastroepiploic is an abortive structure.

B, Same specimen as *A*. The corpus ventriculi has been ablated unmasking the pancreatic vasculature. The rotating procedure of the duodenum and head of the pancreas described in the text has been completed. Note the clarification of the vasculature about the head of the pancreas which has thereby been obtained. The anterior (*AA*) and posterior (*PA*) pancreaticoduodenal arcades form a common stem, the inferior pancreaticoduodenal artery which opens into the first jejunal artery. It is not well known that this is the most common anatomic pattern. As in *A*, the ligament of Treitz (*arrow*) is identified by a straight piece of wire. For key see *A*.

and the pancreas. It was by means of arcades located, respectively, in the pancreas, about the duodenum, and along the transverse colon that the ("constituent") celiac, superior mesenteric, and inferior mesenteric arteries were joined both anatomically and functionally into a common circulatory unit which we have chosen to call the "mesenteric (arterial) circulation."

The vasa recta, though devoid of extraintestinal anastomoses,* communicated with each other in the walls of the small intestine by lateral[4] (longitudinal[3]) and, less constantly, by circumferential anastomoses which in principle could again be viewed as modified arcades (Fig. 9 *A*). Similar pictures were observed in the colon (Fig. 9 *B*). Being visible on the x-ray film with the unaided eye these mural anastomoses were at least 150 micra in diameter.

In general, upon isolated injection of any one of the "constituent" arteries, the arborizations of the other two could also be visualized. As judged by the roentgenographic rendition of the delicate vessels of the stomach, intestine, pancreas, and so forth, such collateral filling was usually better upon isolated injection of the superior mesenteric than of either the celiac or inferior mesenteric arteries, in that order.

Synchronous injection of the celiac and superior mesenteric arteries yielded injection pictures of the inferior mesenteric arborization which were as complete as those obtained by simultaneous injection of all three "constituent" arteries. This was taken as an illustration of observations recorded elsewhere,[7] according to which the inferior mesenteric main stem and its larger (proximal) branches are dispensable.

Everything being equal, it was more difficult to obtain good mural injection in the lower ileum than in any other portion of the intestinal tract. This, we believe, parallels the preferential susceptibility of that segment to infarction upon occlusion of the superior mesenteric main stem.[7]

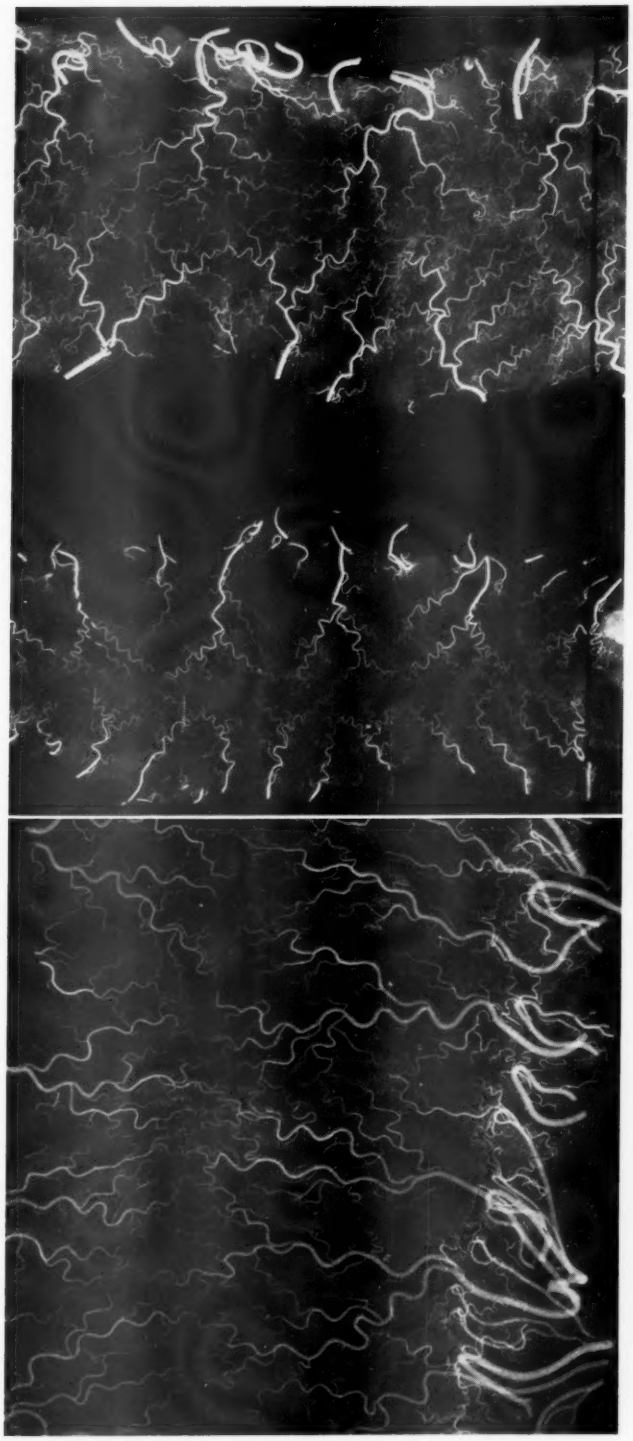
All these observations, of course, merely paraphrased hydrodynamic laws, according to which, with the pressure being constant, the flow of blood (or of injection mass) is directly proportional to the cross-sectional area of the vessel under investigation and indirectly proportional to the viscosity of the vessel contents and the length of the vessel.†

Ligation Experiments.—Upon simple ligation of the main stem of the superior mesenteric artery or of one, two, or even three primary jejunal branches, the quality of injection in the mural vessels of the intestine was not necessarily impaired (Fig. 10). Neither was there necessarily any impairment of filling in the mural vessels after ligation of one or several subsidiary jejunal arcades (Fig. 11). However, ligation of vasa recta to the upper jejunum caused serious, though variable, injection defects in the target intestine (Fig. 12) which, in view of the rich anastomoses existing in the intestinal wall, must be ascribed to high intravascular friction. In several of 10 specimens examined, the collateral potential of the mural vasculature was insufficient to compensate for ligation of even a single vas rectum. In others, it was substantially greater

*According to Noer and associates[5] such extraintestinal anastomoses between vasa recta are normally present in the dog.

†The viscosity of our injection mass is several hundred times greater than that of blood.[6]

A.



B.

Fig. 9.—*A*, Roentgenograms of the mural vasculature of the jejunum (*above*) and ileum. The segments have been opened along the mesenteric insertion. Note the circumferential and arching lateral anastomoses between adjacent vasa recta. *B*, Roentgenogram of the mural vasculature of the colon.

Fig. 10.

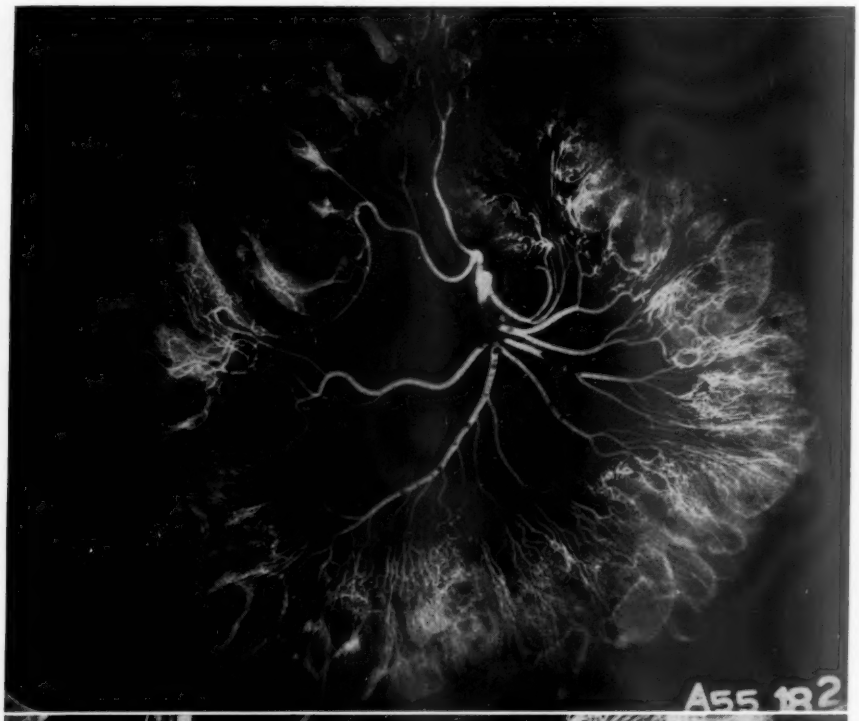


Fig. 11.

Fig. 10.—The superior mesenteric main stem, the ileocolic, and the second and third jejunal arteries have been ligated prior to injection. There is little if any impairment of injection distal to the ligations.

Fig. 11.—(A 55-151) Three successive jejunal arteries have been ligated causing no impairment of injection in the mural vessels.

although never so great as to overcome contiguous ligation of the vasa recta in excess of 4 cm. of intestine as measured along the lesser curvature of the intact jejunal loop. These findings were in accord with those recorded by Doran.[5] Nonetheless, the collateral potential of the mural vessels may be greater in vivo.[5] From our own observations and those of others,[2, 3, 5, 6] it appeared that variations of mural injection after ligation of vasa recta depended on individual variations in the size and number of the mural vessels, on the state of intestinal distention, on the viscosity of the injection mass, and on the injection pressure. Although the vasa recta are not end-arteries in an anatomic sense, they approximate functional end-arteries because of the limited collateral potential displayed by their mural branches. It was probably inadequate injection pressure which led Cokkinis[2] to the erroneous conclusion that "there are absolutely no anastomoses . . . between the ramifying vessels on the gut wall."

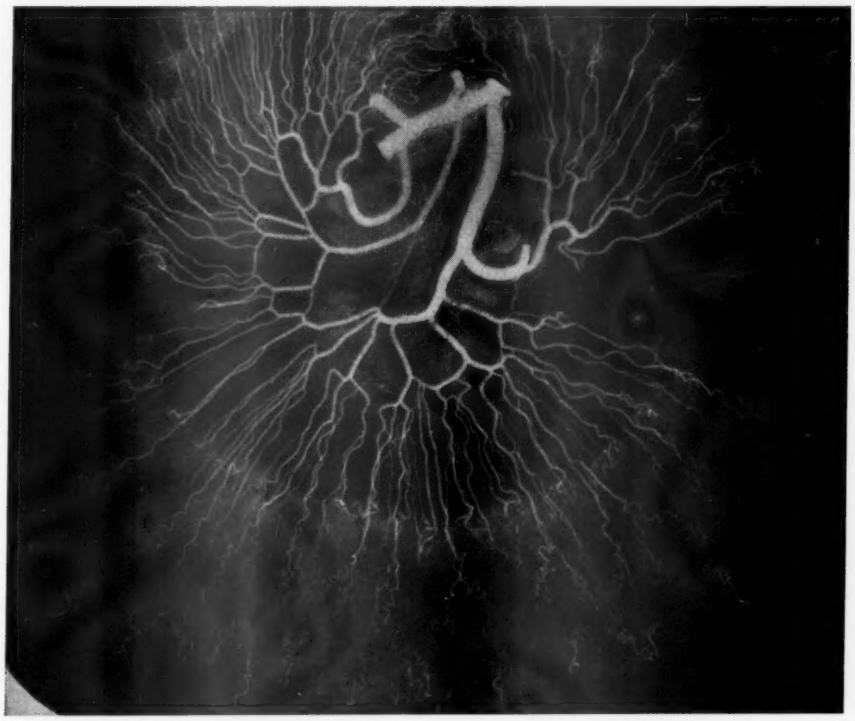


Fig. 12.—(A 55-136) Ligation of vasa recta of a jejunal loop. On the right, a few of the ligated vasa recta have become injected retrogradely via mural anastomoses. There is virtually no retrograde filling of the ligated vessels on the left of the photograph although fewer vasa recta were ligated. Note the adipose tissue arteries in the upper half of the picture.

Anastomoses With Extramesenteric Arteries.—Anastomoses between the mesenteric circulation and extramesenteric arteries could not be traced beyond where they had been severed upon evisceration of the specimen. Their sizes and locations, however, could still be identified by observing any points of leakage during the injection procedure. Most prominent in this respect were the perirectal tissues (communications of the inferior mesenteric with the middle and inferior hemorrhoidal arteries), the cut edges of the hemidiaphragms, and the

inlet of the lower esophagus. Several specimens revealed leakage from the ligamentum teres. Retrograde flow into the abdominal aorta via tiny unnamed vessels was fairly common. Especially the ones opening near the ostium of the inferior mesenteric artery could be shown to supply the posterior parietal subperitoneum and to communicate in turn with tiny adipose tissue vessels given off by the mesenteric arborizations (see next section).

Direct anastomoses with the adrenals (via phrenic branches of the celiac artery) were frequently noted. In a rare specimen, the adipose capsules of the kidney also became injected.

We did not succeed in the eviscerated specimens in injecting the vessels of the pelvic genitourinary structures via the mesenteric arteries.

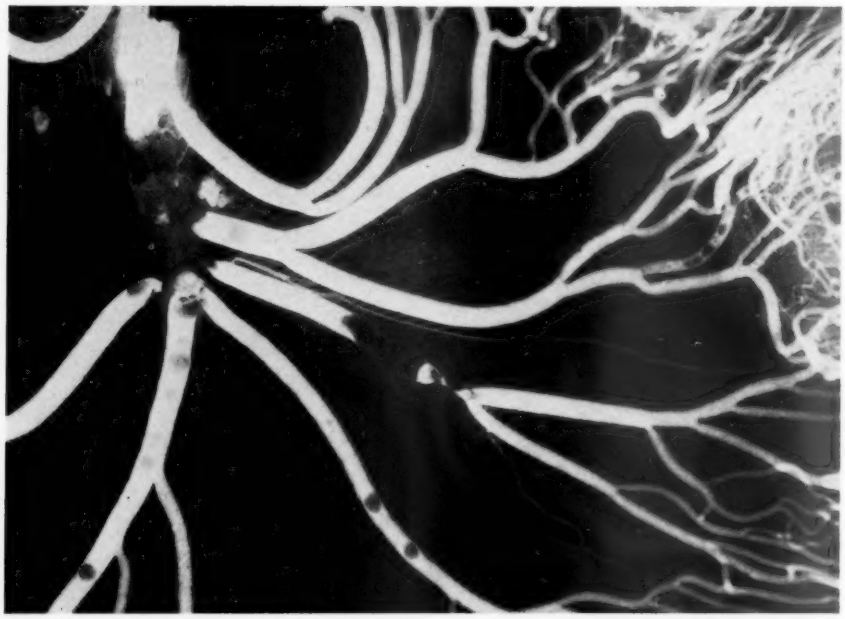


Fig. 13.—A close-up view of Fig. 10, illustrating the relative size and the course of adipose tissue arteries. Note the complete filling of the ligated root of the third jejunal artery via an adipose tissue artery.

Adipose Tissue Arteries.—In addition to the visceral branches, the mesenteric arteries gave rise to a subsidiary system supplying the adipose tissues of the mesenteries themselves. This little-known system was composed of slender vessels arising from and coursing between the main stem arteries and their visceral branches and, less commonly, the aorta itself. They anastomosed with each other in a plexiform rather than an arcading fashion. They often crossed the confines of their parent arcades extending into neighboring or still more distant arcades. They had a tortuous and, occasionally, a corkscrew appearance. Their ability to furnish some measure of collateral supply is illustrated in Fig. 13. They did not seem to increase in diameter with stenosing arteriosclerosis, although they did enlarge considerably about chronic occlusions of visceral branches and main stems in man[7] and after experimental arterial ligation in the monkey.[1]

SUMMARY

A technique for the postmortem study of the mesenteric arteries is described. Following en bloc removal of the abdominal viscera and injection of the vessels with a radiopaque mass, the specimen is triple-partitioned in accordance with the arborizations of the celiac, superior mesenteric, and inferior mesenteric arteries. X-ray arteriograms are being supplemented by dissection of the vessels with scissors.

The celiac, superior mesenteric, and inferior mesenteric arteries are being viewed as constituents of a common circulatory unit here referred to as the "mesenteric circulation." Injection of any one of the constituent arteries permits collateral filling of the other two. Differences in the collateral potential between the constituent arteries have been indicated. The effects of experimental ligation at various levels of arterial branching have been illustrated. For practical purposes, the vasa recta are to be considered functional end-arteries, although they anastomose richly with each other within the wall of the intestine.

Attention is directed to the adipose tissue arteries which supply the mesentery of the small and large intestines and which constitute a little-known subsidiary system of the mesenteric circulation. By their anatomic arrangement and by their ability to enlarge about the sites of mesenteric arterial occlusions, they contribute to the total collateral potential of the mesenteric circulation.

The drawings were executed by Mr. Ralph M. Glazier, Medical Illustrator, Lying-In-Hospital, Boston, Massachusetts.

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DISSECTING ANEURYSM OF THE FEMORAL AND POPLITEAL ARTERY

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AT THE necropsy of a 37-year-old white man who died of bilateral caseous pulmonary tuberculosis and pneumonia it was realized that a previously treated case of acute femoral and popliteal thrombosis was basically a dissecting aneurysm. As a result, the clinical course and the arteriographic characteristics of a dissecting aneurysm of the femoral and popliteal artery could be described. From a similar, even more clear and distinctive, arteriogram a second case became apparent.

These 2 cases and impressions from the literature of 2 others[1, 2] indicate that dissecting aneurysms of peripheral arteries are far less hazardous than of the aorta for two reasons: (1) their accessibility, because of their peripheral location, and (2) the fact of the ischemia being only moderate, in part because the associated reflex vasospasm yields to sympathectomy, as was dramatically evidenced by sympathectomy done as an accessory procedure in the first case and in the second case as a definitive procedure, and in part because the dissecting channel ends by re-entering the main lumen distally, as observed arteriographically in both cases.

CASE REPORT

W. F., Adm. No. 52-33913, a 37-year-old white man, was admitted to the Cook County Hospital complaining of severe pain in the right foot and lower leg and inability to move the toes, beginning a few hours before. Previously the patient was in apparent good health. The right leg appeared cyanotic from the mid-leg down, and on palpation was cold. The femoral pulse was palpable. Oscillations were detectable in the lower third of the thigh, but not below the knee.

Because of the impression of an acute, recent occlusion, the popliteal artery was opened. Fragments of a thrombus were removed, followed by the flow of pulsating blood. No bleeding occurred from the distal side of the opened artery. The artery was then closed. Intermittent intravenous heparin was administered postoperatively. The patient became free of pain, the leg warm down to the foot, and the toes could be readily moved. The cyanosis decreased. One-half unit oscillations were detected in the middle third of the right leg compared to two units in the other leg.

Because of the gradual return of coldness, numbness, and cyanosis, a femoral arteriogram was done one week postoperatively. The femoral and popliteal arteries were well visualized, but a central radiolucency in the lumen of the popliteal artery without apparent obstruction was observed. This central radiolucency and the associated lateral edges of the artery outlined by the injected dye later (at necropsy) proved to be due to a dissecting aneurysm. The "streaked" distribution of the dye—alternating with longitudinal zones containing no dye—indicated the multiple channels within the dissecting artery as observed in the upper and middle portions of the femoral artery (Fig. 1).

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A lumbar sympathectomy was done, whereupon this foot immediately became much warmer, and one unit of oscillation was detectable below the knee. Rapid improvement followed and the patient walked out of the hospital unassisted, 13 days after lumbar sympathectomy and 23 days postarteriotomy and thrombectomy.

A. *B.*

Fig. 1.—*A*, Femoral arteriogram of W. F. on July 2, 1952. The dye in the superficial femoral artery has a streaked appearance in the upper and midportions and in the midpopliteal region. The streaked outline indicates the alternating dissecting and original channels in the artery. *B*, The lower part of the popliteal artery. The terminal portion of the dissection can be seen at the approximate level of the joint space.

Approximately one month later the patient was readmitted with impending gangrene of the right foot. Two days before, a "throbbing" was noticed in the right foot, and 2 hours prior to admission, a sudden onset of excruciating pain in this foot and leg, with inability to move the toes, and shortly thereafter also numbness. The patient was restless and crying with pain. Pulse was 120 and regular, blood pressure 132/80. The right leg and foot appeared ashen gray on elevation and markedly cyanotic in both the dependent and horizontal positions. A critical temperature level was detectable just below the knee. No pulsations nor oscillations were detectable distal to mid-thigh. An arteriogram revealed an occlusion approximately midway down the superficial femoral, with collaterals extending a short distance beyond. Acute arterial thrombosis was considered, and the patient immediately was reoperated upon.

Fig. 2.

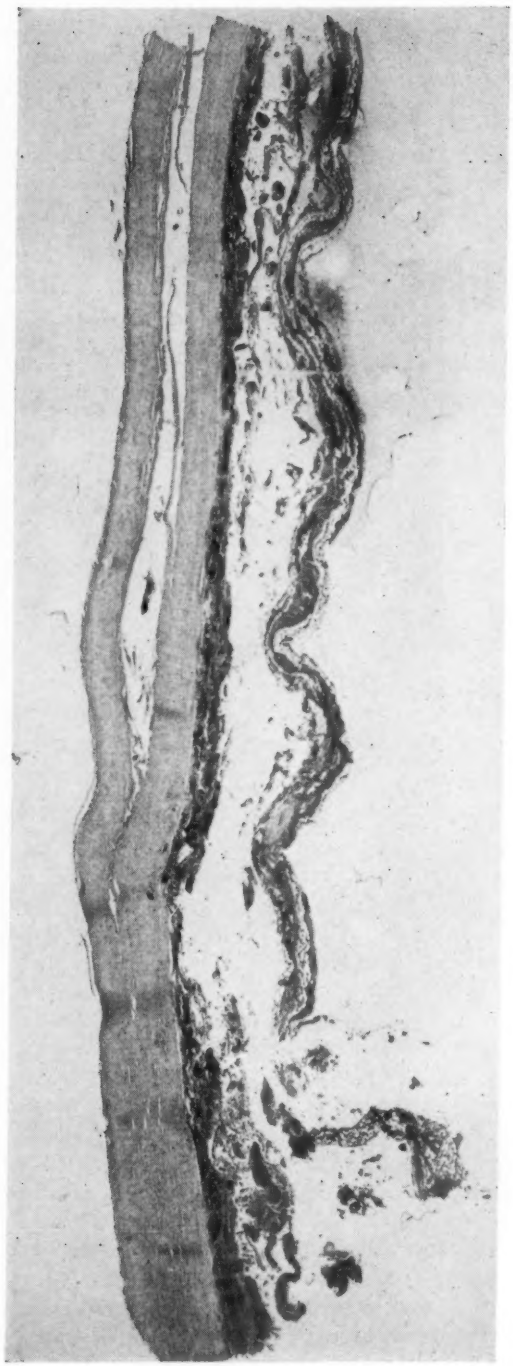

Fig. 3.

Fig. 2.—Central, originally normal, channel is opened. The dissecting channel can be observed at either side of the "normal" channel.

Fig. 3.—Histologic longitudinal section showing space of dissection in the media part of arterial wall. (×8.)

The lower part of the femoral artery was exposed down to the popliteal. With needle and syringe a lumen was found in this zone but contained no blood. This probably was the original lumen, internal to the dissecting channel. Next, the popliteal artery was opened. Recent thrombi were found by aspiration. The superficial femoral in its lower part was also incised and recent thrombi were aspirated from higher up in the femoral through this lower segment. The vessel was then closed. Postoperatively the patient was maintained on anticoagulant therapy. Postoperatively the patient rapidly improved. The foot became pink, and he walked out of the hospital unassisted.

After 7 months, during which time he had been working at his usual job as a timekeeper, he was readmitted for a severe acute pulmonary infection from which he died in 3 days. During this last admission the right foot was observed to be as warm as the left, though without a dorsalis pedis pulse on the right.

At necropsy, bilateral pulmonary fibrocaseous tuberculosis in the upper lobes, and confluent bronchopneumonia of the lower left lobe (P.M. No. 385-53, done on April 1, 1953) were found. Permission was obtained to remove the right femoral and popliteal arteries. When this arterial trunk was opened an irregular longitudinal dissection was observed (Fig. 2). Histologic sections show the dissection in the media (Fig. 3).

Fig. 4.—Femoral arteriogram of second patient showing the superficial femoral artery dissected through most of its course with moderate number of collaterals from profunda to genicular branch bridging this partial occlusion by dissection. Central radiolucency is readily observable.

A survey of our previous arteriograms revealed another case with the same arteriographic characteristics of a dissecting aneurysm involving the superficial femoral artery, even more clearly than the first case. A central radiolucency is noted from the upper level of the superficial femoral down to the popliteal

level (Fig. 4). The lateral edges of this artery appear well outlined. In the lower femoral the dye appears to fill the entire lumen for a short distance, and then distally appears to pass only along the lateral edge of the artery. It appears that the dye and the blood stream follow the dissecting channel. Moderate to profuse collaterals extend between the profunda femoris and branches of the popliteal artery bridging the zone of dissection. This second patient, a 52-year-old white man, was admitted to the Cook County Hospital with the history that, 8 days before, he had developed a sudden severe pain in the left leg accompanied by coldness of the foot and inability to use the left foot. Four days later, the left foot became cyanotic. Past history and review of systems were essentially negative. Following a lumbar sympathetic block, the foot became much warmer. An arteriogram taken at this time is described above. A left lumbar sympathectomy was then performed, whereupon the leg and foot became warmer than the right, and was no longer painful. The patient shortly thereafter was discharged, walking out of the hospital after a rapid recovery, without complaint.

DISCUSSION

Dissecting aneurysms of the femoral and/or popliteal artery are extremely rare. Giles[1] in 1945 reported a case diagnosed at operation. The considerably dilated dissecting channel resulted in an inflammatory reaction. Upon incision for drainage of the "abscess," the dilated aneurysmal sac was recognized and closed. A good recovery was made although no dorsalis pedis pulse was detectable. This patient, like the others, experienced moderate-to-severe pain but remained active for several days after the onset and had no pertinent past history. A case of dissecting aneurysm of the femoral artery with the diagnosis based only on clinical impression, as reported by Kositchek,[2] was treated successfully by sympathectomy alone. This result parallels those in our experience, especially in the second case reported here in which lumbar sympathectomy only was done.

SUMMARY

1. A case of a dissecting aneurysm of the superficial femoral and popliteal artery verified both grossly and microscopically is herein reported for the first time.

2. This dissecting aneurysm became complicated by acute thrombosis on two separate occasions, for which thrombectomy was accomplished each time.

3. For the first episode of acute thrombosis a lumbar sympathectomy was done with excellent results, subsequent to the thrombectomy, indicating the occurrence of considerable reflex vasospasm.

4. At necropsy (the patient died of pulmonary tuberculosis and pneumonia), the dissecting aneurysm of the femoral and popliteal artery was discovered.

5. As a result, the arteriographic characteristics of a dissecting aneurysm became recognizable.

6. The second case reported here is based on the clear arteriographic characteristics of a dissecting aneurysm, as established by the first case, and demonstrates the effectiveness of lumbar sympathectomy.

7. The presenting symptoms are considerable pain in the extremity and moderate ischemia.

8. The relatively benign course of dissecting aneurysm of peripheral arteries, and the excellent result which may be obtained, at least temporarily, by lumbar sympathectomy are demonstrated in these 2 cases.

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EXPERIMENTAL EVALUATION OF INTERNAL MAMMARY ARTERY LIGATION AS A METHOD OF MYOCARDIAL REVASCULARIZATION

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COMMUNICATIONS between the internal mammary arteries and the coronary system have been previously demonstrated.[11, 12, 16, 17, 20, 21] On the basis of this knowledge, Fieschi, in 1939, devised the procedure of ligation of the internal mammary arteries as a method to increase the blood supply to the ischemic myocardium.[2] Since 1955, when Battezzati, Tagliaferro, and DeMarchi[2] reported favorable results following the clinical application of internal mammary artery ligation, many experimental and clinical accounts have appeared in the medical literature.[1-5, 7, 10, 13, 14, 18, 19] However, doubt continues to exist regarding a sound physiologic basis for the clinical success. Three experimental approaches have been utilized in an attempt to determine whether or not internal mammary artery ligation increases collateral blood flow to the heart.

METHOD

Forty dogs with an average weight of 33.9 pounds were used. General anesthesia was produced by the intravenous injection of pentobarbital sodium (12 mg. per pound). Respiration was maintained with compressed room air via an endotracheal tube.

1. In the first experiment, an attempt was made to determine if ligation of the internal mammary arteries afforded the animal a degree of protection against acute coronary occlusion. Thirty animals were utilized with 10 of these comprising the control group. Coronary occlusion was produced in 10 dogs 30 minutes following ligation of the internal mammary arteries at the level of the second intercostal space. In the remaining 10, the internal mammary arteries were divided 2 weeks prior to ligation of the coronary artery.

The chest was entered through the left fourth intercostal space and the pericardium was opened. The anterior descending branch of the left coronary artery was ligated immediately distal to the septal branch (Fig. 1).

2. Five dogs were used in the second experiment and a technique was devised to measure the local effects of acute occlusion of the internal mammary artery on arterial pressure and flow (Fig. 2).

The chest was entered through a longitudinal sternum-splitting incision and the internal mammary artery was exposed. The second anterior intercostal

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artery was identified for a distance of 5 cm. Heparin (1 mg. per kilogram) was administered intravenously. End pressures and blood flow were measured through a No. 90 polyethylene tube inserted into the second intercostal vessel, 5 cm. from the internal mammary artery. Lateral pressures were obtained from the internal mammary artery through a No. 90 polyethylene catheter inserted into the third intercostal artery. Aortic pressure was monitored through a No. 200 polyethylene catheter inserted into the femoral artery. A nontraumatizing clamp was used at intervals to obstruct the internal mammary artery between the third and fourth intercostal arteries to determine the effect of internal mammary occlusion on pressure and flow in the internal mammary artery and second intercostal artery.

Fig. 1.

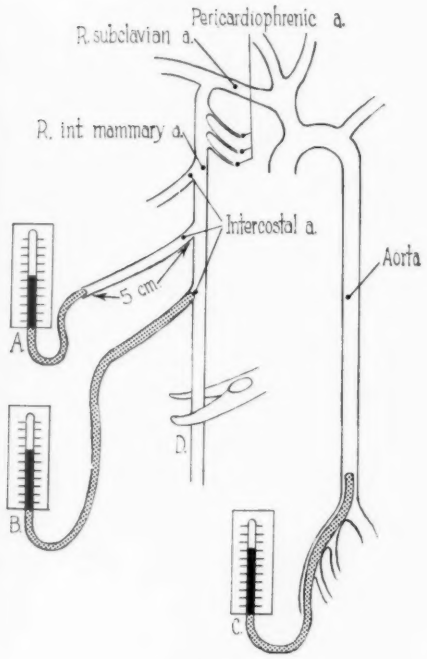

Fig. 2.

Fig. 1.—Photograph showing site of occlusion of the anterior descending coronary branch immediately distal to the septal branch.

Fig. 2.—Diagrammatic illustration of the technique employed to measure pressures and flows in the internal mammary artery system. *A*, Catheter used to measure "end" pressure and flow in the second intercostal artery. *B*, Catheter used to measure "lateral" pressure in the internal mammary artery. *C*, Catheter used to monitor aortic pressure. *D*, Clamp used to occlude internal mammary artery.

3. In the third experiment, the acute effect of bilateral internal mammary artery occlusion on retrograde pressure and flow in a major coronary artery was studied in 5 dogs. The chest was entered through the left fourth intercostal space. The internal mammary arteries were occluded intermittently with atraumatic clamps at the level of the second intercostal space and heparin (1 mg. per kilogram) was injected intravenously. Retrograde coronary artery pressures and flows were obtained through a No. 90 polyethylene catheter inserted distally into the anterior descending branch of the left coronary artery. Simultaneous aortic pressures were monitored through a No. 200 polyethylene catheter inserted through the femoral artery (Fig. 3).

RESULTS

1. In the initial group, 90 per cent of the control animals died. The mortality rate of the 20 animals "protected" by ligation of the internal mammary arteries was 70 per cent. Irreversible ventricular fibrillation developed at the time of coronary occlusion in 60 per cent of the control group and 50 per cent of the "protected" animals. All remaining mortalities occurred within 72 hours following ligation of the coronary artery. The time interval between internal mammary ligation and coronary occlusion produced no difference in the survival rate. The size of myocardial infarction* caused by coronary obstruction was not significantly affected by division of the internal mammary arteries (Table I).

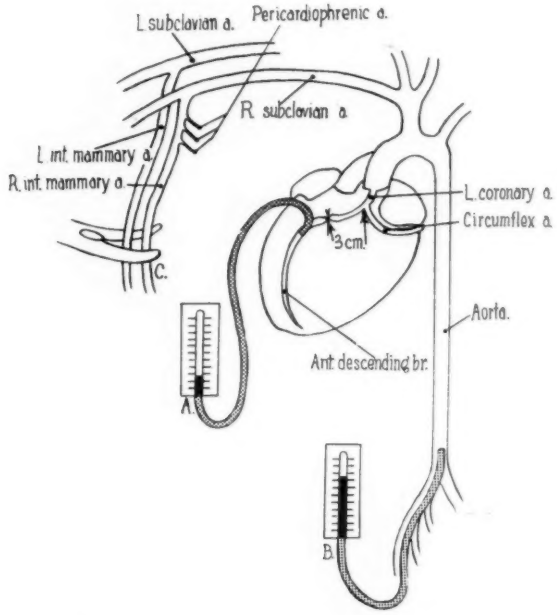

Fig. 3.—Diagrammatic illustration of technique employed to measure effect of bilateral internal mammary artery occlusion on retrograde coronary pressure and flow. *A*, Catheter used to measure retrograde pressure and flow in coronary artery. *B*, Catheter used to monitor aortic pressure. *C*, Clamp used to occlude internal mammary arteries.

TABLE I. EFFECT OF CORONARY OCCLUSION FOLLOWING BILATERAL INTERNAL MAMMARY ARTERY LIGATION

	CONTROL GROUP	INTERNAL MAMMARY ARTERIES LIGATED		
		30 MIN. BEFORE	2 WEEKS BEFORE	TOTAL
Number of dogs	10	10	10	20
Died at operation	6 (60%)	5 (50%)	5 (50%)	10 (50%)
Died in 72 hours	3 (30%)	2 (20%)	2 (20%)	4 (20%)
Infarct ratio*	60.0	56.8	58.3	57.6
Survivors	1 (10%)	3 (30%)	3 (30%)	6 (30%)

*Infarct ratio $= \frac{\text{area of infarct}}{\text{area of ventricle}} \times 100$.

2. In the second experiment, no pressure changes occurred either in the internal mammary artery or in the intercostal branch following acute internal

*Infarct size was compared by use of a formula described by Goldman[5]:

$\frac{\text{area of infarct}}{\text{area of ventricle}} \times 100 =$ infarct ratio (IR).

mammary occlusion, nor was volume flow through the anterior intercostal artery significantly affected. After 30 minutes of sustained occlusion of the internal mammary artery, the mean pressure (average) decreased from 113 mm. Hg to 111 mm. Hg in the internal mammary artery, and from 106 mm. Hg to 105 mm. Hg in the intercostal artery. These changes were paralleled by a decrease in the aortic pressure of 3 mm. Hg. The average flow through the intercostal artery was 17.9 c.c. per minute with the internal mammary artery open, and 18.3 c.c. per minute with the mammary occluded (Table II). An example of the pressure tracings and flow rates is reproduced graphically in Figs. 4 and 5.

TABLE II. LOCAL EFFECT OF ACUTE OCCLUSION OF THE INTERNAL MAMMARY ARTERY

NUMBER OF DOGS	AVERAGE WEIGHT (LBS.)	ARTERY	PRESSURE (MM. Hg)			FLOW (C.C./MIN.)	
			INT. MAM. OPEN	INT. MAM. OCCLU. (IMMEDIATE)	INT. MAM. OCCLU. (30 MIN.)	INT. MAM. OPEN	INT. MAM. OCCLU. (15 MIN.)
5	37.6	Int. mam.	113	114	111	17.9	18.3
		Intercostal	106	106	105		
		Aorta	125	125	122		

3. In the third experiment, bilateral occlusion of the internal mammary arteries failed to produce any variation in retrograde coronary artery pressure or flow (Figs. 6 and 7). With the internal mammary arteries obstructed for periods of 15 to 25 minutes, the retrograde pressure in the anterior descending branch of the left coronary artery remained constant at 19 mm. Hg. Retrograde coronary flow averaged 2.0 c.c. per minute, with or without the mammaries occluded (Table III).

TABLE III. EFFECT OF OCCLUSION OF THE INTERNAL MAMMARY ARTERIES ON RETROGRADE CORONARY ARTERY PRESSURE AND FLOW

NUMBER OF DOGS	AVERAGE WEIGHT (LBS.)	ARTERY	PRESSURE (MM. Hg)			FLOW (C.C./MIN.)	
			INT. MAM. OPEN	INT. MAM. OCCLU. (IMMEDIATE)	INT. MAM. OCCLU. (15-25 MIN.)	INT. MAM. OPEN	INT. MAM. OCCLU. (15 MIN.)
5	30.3	Coronary (retrograde pressure)	19	19	19	2.0	2.0
		Aorta	124	122	124		

DISCUSSION

Glover and his associates[7] reported that the mortality rate following experimental coronary occlusion decreased from 93 per cent in the control group to 42 per cent in dogs "protected" by ligation of the internal mammary arteries. In contradistinction, Sabiston and Blalock[18] observed a mortality rate of 78 per cent if coronary obstruction was produced at the time of internal mammary ligation, and 93 per cent if coronary occlusion was delayed for 30 days following division of the internal mammary arteries. The mortality rate of 70 per cent in the study presented here is in agreement with that reported by Sabiston and Blalock,[18] which indicates that bilateral internal mammary artery ligation does not afford the heart significant protection against acute coronary occlusion.

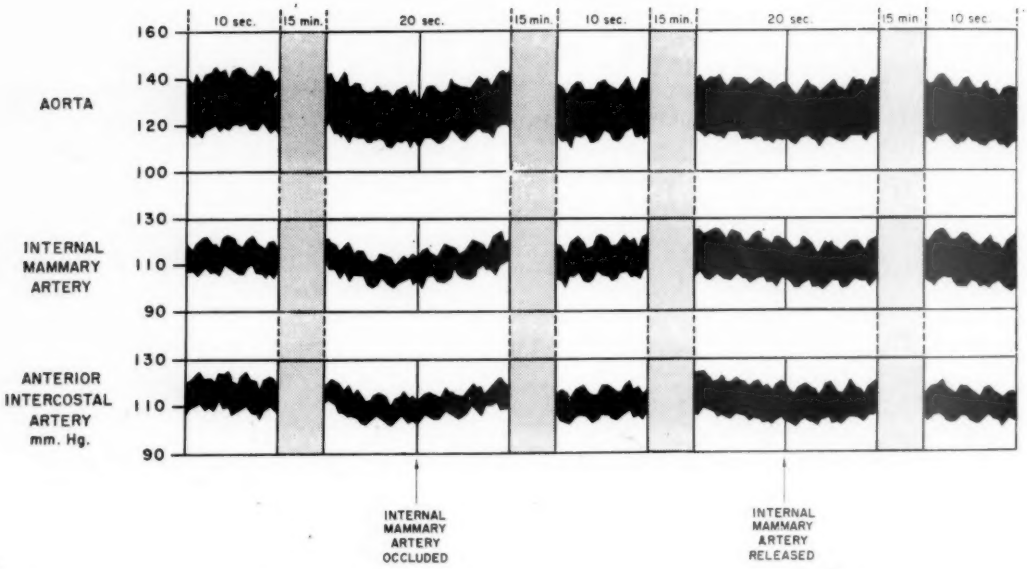

Fig. 4.—Pressure tracing demonstrating the effect of internal mammary occlusion on pressure in the internal mammary artery and a tributary.

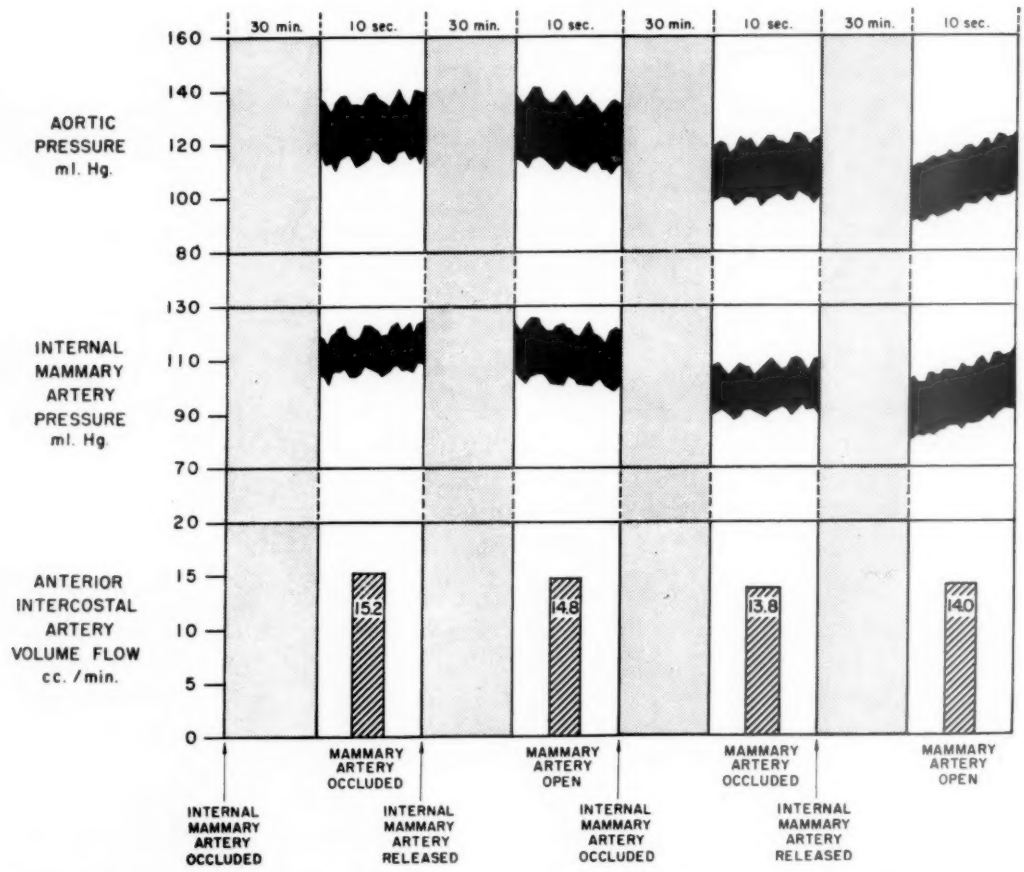

Fig. 5.—Pressure tracing demonstrating the effect of internal mammary occlusion on flow in a tributary of the internal mammary artery.

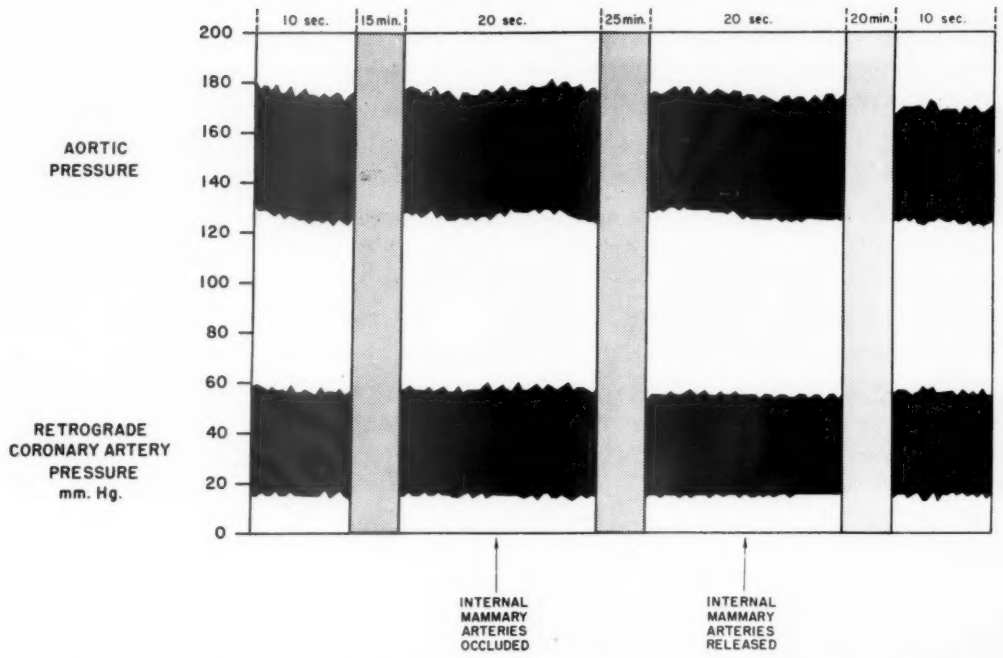

Fig. 6.—Pressure tracing demonstrating the effect of bilateral internal mammary artery occlusion on coronary artery retrograde pressure.

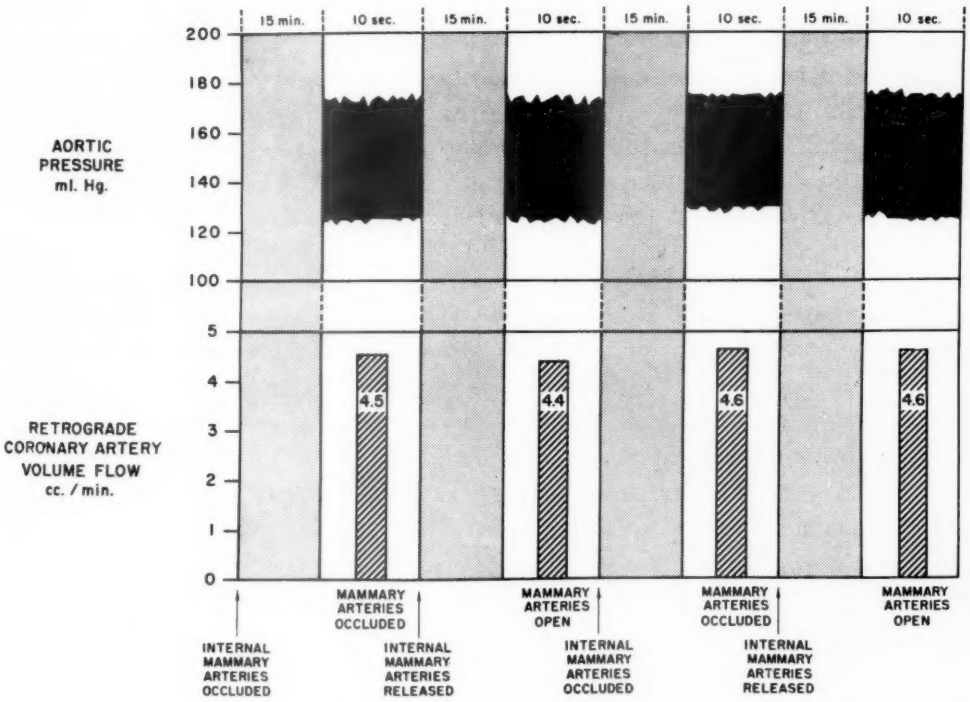

Fig. 7.—Pressure tracing demonstrating the effect of bilateral internal mammary artery occlusion on coronary artery retrograde flow.

Proponents[2, 4, 7] of this technique of increasing the collateral blood supply to the heart maintain that hypertension develops proximal to the point of occlusion of the internal mammary artery. This increase in pressure is thought to cause distention of the pre-existing collaterals between the internal mammary artery and the coronary system which results in an increase in the volume blood flow to the myocardium.

Glover[7] observed a sustained rise in end pressures of 14 mm. Hg in the occluded internal mammary artery. Employing an artificial reproduction of the internal mammary pericardiophrenic artery system composed of plastic tubing, Taber and Marchioro[19] reported an increase in the pericardiophrenic flow and pressure following occlusion of the internal mammary artery.

In our evaluation, many variables were avoided by the direct application of the experiment to the vessels in question. Pressures and flow were measured in the second intercostal artery in addition to the internal mammary artery which were comparable to the pericardiophrenic artery and no increase in pressure or flow was demonstrated following occlusion of the internal mammary artery.

With the experimental animal on total cardiac bypass, Lord and his co-workers[14] failed to elicit a significant increase in the collateral blood flow to the heart 6 weeks following internal mammary ligation. Blair and colleagues[3] likewise found no increase in collateral flow. Similar conclusions were reported by Griffin and co-workers[10] who determined the effect of bilateral internal mammary ligation following the injection of albumin, tagged with radioactive iodine, into the internal mammary arteries.

The technique of measuring retrograde coronary pressure and flow described by Mautz and Gregg[15] has been employed extensively as a means of determining collateral blood flow to the heart.[6, 9] In our investigation, this method offered further evidence to indicate that acute ligation of the internal mammary arteries does not increase the collateral blood flow to the heart.

SUMMARY AND CONCLUSIONS

Three experimental approaches were utilized to determine whether or not internal mammary artery ligation increases collateral blood flow to the heart.

1. The mortality rate following ligation of a major coronary artery was employed to judge the degree of protection afforded the heart. A mortality rate of 90 per cent occurred in the control group. Following ligation of the internal mammary arteries, the mortality rate was 70 per cent. These results are not indicative of statistically significant myocardial protection.*

2. A technique was devised to measure pressures simultaneously in the internal mammary artery and pressures and flows in a tributary of this vessel which is comparable to the pericardiophrenic artery. Occlusion of the internal mammary artery distal to the tributary did not significantly affect the pressures in the internal mammary artery or in the tributary, neither did it appreciably increase the volume flow through the tributary.

*X^2 (with Yates' correction) = 0.2; P = .70.

3. The third method of evaluation consisted of measuring the acute effects of bilateral internal mammary artery ligation on the retrograde pressures and flows of an occluded coronary artery. No significant change in either measurement occurred when the internal mammary arteries were totally obstructed.

No evidence was obtained from these studies to demonstrate that bilateral internal mammary artery ligation increases the collateral blood supply to the myocardium.

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A COMPARATIVE STUDY OF AORTIC OCCLUSION ALONE AND OF POTASSIUM CITRATE ARREST DURING CARDIOPULMONARY BYPASS

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DURING cardiopulmonary bypass for correction of intracardiac anomalies, it is frequently necessary to utilize some adjunctive measure to control coronary circulation temporarily. Otherwise, coronary sinus flow may prevent adequate visualization of the intracardiac defect and account for excessive blood loss. The first method used to overcome these problems during bypass was intermittent aortic occlusion.[6] However, this method now has been replaced for the most part by chemically induced cardiac arrest. This report is concerned with a comparative study of the effects of aortic occlusion alone and of potassium citrate arrest during cardiopulmonary bypass in dogs.

METHODS

Mongrel dogs weighing from 12 to 18 Kg. were anesthetized with intravenous sodium Pentothal. An endotracheal airway was maintained. The chest was entered through a right-sided intercostal incision, and the lungs were inflated periodically with 100 per cent oxygen. Catheters were placed in the superior and inferior venae cavae through incisions in the right auricular appendage. Another catheter was passed into the terminal aorta through a femoral arteriotomy.

During bypass, the venae cavae were occluded within the pericardial sac and the venous blood was allowed to drain by gravity into a reservoir. Blood from the reservoir was perfused by a Sigmamotor pump through a DeWall-type bubble oxygenator. A mixture of 95 per cent oxygen and 5 per cent carbon dioxide was bubbled through the blood at the rate of 1 liter per 150 c.c. blood flow per minute. After passing through the oxygenator, the blood was pumped through two Baxter filters and returned to the animal through the arterial catheter. Periodic insufflation of the lungs was continued during bypass. Rectal temperature was recorded continuously with a thermocouple and heating pads, used in an attempt to keep the animal euthermic.

Systemic arterial blood pressure and a standard lead of the electrocardiograms were recorded on a Sanborn Poly-viso amplifier before, during, and after bypass.

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The animals in this study were divided into two groups of 9 each. Cardiac arrest was induced with potassium citrate in all animals in Group I. Aortic occlusion without cardiac arrest was used in all animals in Group II. In each group the perfusion rate was 40 c.c. per kilogram per minute in 8 dogs and 60 c.c. per kilogram per minute in 1 dog.

In Group I a 2.5 per cent solution of potassium citrate in oxygenated blood was used to induce cardiac arrest. The solution was injected as rapidly as possible through a No. 18-gauge needle inserted into the ascending aorta proximal to an occluding forceps. The total amount of solution required to produce arrest varied from 10 to 15 c.c. In the dogs perfused at the 40 c.c. rate, the total duration of cardiac arrest was 5 minutes in 4 animals, 10 minutes in 3 animals, and 20 minutes in one animal. The duration of cardiac arrest in the dog perfused at the 60 c.c. rate was 10 minutes.

In Group II the aorta was occluded for 5 minutes in each animal.

A right ventriculotomy, measuring approximately 3 cm., was made in all animals during cardiac arrest or aortic occlusion alone. This incision was closed after cardiac action appeared to return to normal, if it did so. Otherwise, the incision was left open or partially open to allow the escape of blood returning to the right ventricle. Blood escaping from the ventricular incision was returned to the pump-oxygenator apparatus through a separate suction pump.

RESULTS

Group I.—Cardiac activity reappeared in all 9 animals from 30 seconds to 3 minutes following release of the aortic clamp. Two of the animals perfused with 40 c.c. per kilogram per minute developed a normal sinus rhythm with an effective beat. Of the remaining 6 animals perfused at the same rate, 3 developed ventricular fibrillation and 3 a normal sinus rhythm with an ineffective beat. The animal perfused with 60 c.c. per kilogram per minute developed a normal sinus rhythm but an ineffective beat.

The 2 animals with a normal sinus rhythm and effective beat following arrest required no further therapeutic procedure.

The 3 animals who developed ventricular fibrillation following arrest were treated initially by increasing the flow rate by 20 c.c. per kilogram per minute and the flow of oxygen and carbon dioxide by 2 liters per minute. However, none of the animals responded after 10 minutes of increased flow rates so that repeat arrest with potassium citrate was carried out. In one animal in whom cardiac arrest was induced a second time, the rhythm reverted to normal sinus with an effective beat after restoration of coronary flow. In another animal, the rhythm also reverted to normal sinus but the beat was ineffective. The third animal with ventricular fibrillation developed recurrent fibrillation following repeat arrest.

The 4 animals with a normal sinus rhythm but ineffective beat were maintained on bypass without any noticeable increase in contractile force 10 minutes after cessation of arrest. Attempts to restore the contractile force to normal by injection of 20 c.c. of molar sodium lactate into the left ventricle were unsuccessful in all animals. A 10 per cent solution of calcium chloride was then

given by left ventricular puncture. Two of the animals developed intractable ventricular fibrillation after injection of 10 c.c. The other 2 animals showed no response to a similar injection of 10 c.c.

Group II.—In all 9 animals, the heart continued to beat with a normal sinus rhythm during and after the period of aortic occlusion. In 2 dogs there was a progressive decrease in the rate and strength of beat during the period of occlusion, but the cardiac action returned to normal quickly after release of the aortic clamp. All of the animals appeared to have normal cardiac action at the end of the operative procedure.

DISCUSSION

A comparison of cardiac activity following the induction of potassium citrate arrest and the use of aortic occlusion alone shows a decided difference in the incidence of ventricular fibrillation and ineffective cardiac action (Table I). The high incidence of fibrillation and ineffective cardiac action associated with potassium arrest is particularly significant in view of the poor results obtained with treatment of these conditions. Possibly ventricular fibrillation might have responded better to electric shock than to repetition of arrest. Even so, there still remains the problem of the heart with a normal sinus rhythm but ineffective beat which in this series followed arrest as often as fibrillation.

TABLE I. CARDIAC ACTIVITY FOLLOWING CARDIAC ARREST

METHOD OF ARREST	NUMBER OF DOGS	NORMAL SINUS RHYTHM WITH EFFECTIVE BEAT	VENTRICULAR FIBRILLATION	NORMAL SINUS RHYTHM WITH INEFFECTIVE BEAT
Potassium citrate	9	2	3	4
Aortic occlusion alone	9	9	0	0

The most common objection to aortic occlusion alone as a means of controlling coronary circulation is that the heart continues to beat and necessarily continues to require oxygen. Consequently, it is feared that hypoxic changes may occur during aortic occlusion with resultant arrythmias or weakness of contractile force. No such changes were apparent in this study in the group of 9 dogs who underwent 5 minutes of aortic occlusion. Moreover, temporary aortic occlusion has been used by Cooley[1] with good results in more than 100 patients. Possibly the prevention of hypoxic changes during aortic occlusion is related to a lowered oxygen requirement due to the decreased work load of the heart during bypass. Periodic insufflation of the lungs may also be of benefit during aortic occlusion by increasing bronchial blood flow, and thereby increasing coronary circulation.

It would appear from the results of this experiment that the use of potassium citrate arrest in dogs during cardiopulmonary bypass increases significantly the hazards of operation. This is in agreement with the work of Kaplan and associates,[4] who reported a 50 per cent mortality in dogs subjected to cardiac arrest with potassium citrate as compared to a 10 per cent mortality in dogs

not subjected to cardiac arrest during bypass. The most common cause of death in the animals subjected to cardiac arrest was failure of the heart to resume its normal rhythm. It is recognized that the discrepancy between these experimental results and the clinical successes reported with potassium citrate arrest[3, 5] may be due in part to species differences. However, a significant number of arrythmias[2] and hearts with a weak contractile force which did not respond to the usual methods of treatment have been observed clinically after potassium citrate arrest. Temporary aortic occlusion would seem to be a much simpler and safer method for controlling coronary circulation for the time intervals used in these experiments under the conditions described.

SUMMARY

1. Cardiac arrest with potassium citrate was induced in a group of 9 dogs during cardiopulmonary bypass. Eight of the dogs were perfused with 40 c.c. per kilogram per minute and one dog was perfused with 60 c.c. per kilogram per minute. The duration of arrest was 5 minutes in 4 dogs, 10 minutes in 3 dogs, and 20 minutes in 1 dog.

2. Temporary aortic occlusion alone was produced in a similar group of 9 animals. The aorta was occluded for 5 minutes in each animal.

3. Seven of the 9 animals who were subject to cardiac arrest with potassium citrate developed either ventricular fibrillation or ineffective cardiac action following arrest. In only one of these 7 animals could the cardiac action be reverted to a normal sinus rhythm with an effective beat.

4. Ventricular fibrillation or ineffective cardiac action did not occur in any of the animals after 5 minutes of sustained aortic occlusion alone.

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COSTAL CHONDRITIS AND PERICHONDRITIS

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COSTAL chondritis, an infrequently discussed entity in medical literature, is usually characterized by a persistently draining sinus of the thoracic wall that is exquisitely painful to the patient. In order to call attention to the subject generally, to see whether the incidence of the disease has increased with the increase in the number and variety of surgical procedures being done through the chest, and to see whether anything could be added to the literature regarding its etiology and pathogenesis, all histories indexed under the heading of costal chondritis at the Mayo Clinic were reviewed. Specimens were then studied both in the gross form and microscopically, and cases in which the diagnosis was verified were included in the study.

ANALYSIS OF CASES

The accumulated series from the clinic consisted of 17 cases. Eleven of the patients were men and 6 were women, with the largest number being in the sixth decade of life (Table I).

TABLE I. AGE AND SEX DISTRIBUTION OF 17 PATIENTS HAVING COSTAL CHONDRITIS

AGE (YEARS)	SEX		TOTAL
	MALES	FEMALES	
0 to 10	–	–	–
11 to 20	–	–	–
21 to 30	1	–	1
31 to 40	1	–	1
41 to 50	3	2	5
51 to 60	4	3	7
61 to 70	1	1	2
71 to 80	1	–	1

Symptoms in all cases were those of intermittently or persistently draining sinuses of the anterior wall of the chest, and usually were accompanied by considerable pain. In three exceptions to this general rule, the patients came to the clinic, each with an area of inflammation and induration of the chest wall, one described as being "of golf-ball size" and containing frank pus. Presumably all of the lesions would have drained spontaneously had sufficient time been permitted.

In an attempt to determine what factors contributed to the development of costal chondritis, it was found that in 5 cases onset of the disease followed radical mastectomy. In 3 of the 5, roentgen therapy also had been administered

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after operation. In 2 cases chondritis developed after bouts of pneumonia and in 2 it followed surgical procedures on the biliary tract; in one of the latter 2 cases complications resulted from drainage of empyema of the thorax. In another case chondritis followed drainage of a subdiaphragmatic abscess secondary to an operation on the stomach, and in 2 cases a fairly definite history of trauma was elicited. In 4 cases the chondritis apparently occurred spontaneously, and in all of these positive bacteriologic evidence of tuberculosis was found from material cultured from the sinus tract, from studies of sputum, or from examination of fluid obtained by thoracentesis.

In one case chondritis resulted indirectly from a transsternal approach to a congenital cardiac defect, the postoperative course (elsewhere) being complicated by the development of empyema.

Bacteriologic studies of material cultured from the sinus tracts or material removed at operation was available in seven cases. *Staphylococcus aureus, Diplococcus pneumoniae,* hemolytic streptococci, *Escherichia coli,* Cornyebacterium, and Pseudomonas were organisms found either singly or in various combinations in the 7 cases. Pseudomonas was the most frequent offender, and these organisms were found in 3 of the 7 patients. The hemolytic streptococci were cultured from the sinus of a patient whose sputum showed positive evidence of tuberculosis and who was dismissed to a sanatorium for further treatment.

The location of the chondritis in those patients in whom definite precipitating factors were involved was as one might expect. The involved cartilages were in the region to which radiation had been directed, or near the site of drainage of an abscess cavity. In the 4 cases in which tuberculosis was incriminated, the cartilages excised were as follows: right fifth; right fourth and fifth; left third followed later by the left sixth; left fourth through the seventh cartilages, the lower portion of the sternum and 1 inch of cartilage at the same level from the right side. In the 2 patients who showed evidence of trauma the left sixth, seventh, and eighth cartilages were involved in one, and the left tenth cartilage in the other.

The formalin-fixed specimens generally consisted of small-to-medium bits of cartilage, bone, and adjacent tissue. The cartilage, where abnormal, showed single to multiple yellowish-white areas on cross section, often with a definite sinus tract present in the center of the discolored areas. In 2 cases, the tract extended into an adjacent rib. The external surfaces were often irregularly eroded in a manner to which the term "moth-eaten" could easily be applied.

Microscopically, the general appearance of the sections made from the grossly involved specimens were all essentially the same. In some portions the cartilage was normal. The inflammatory reaction was located peripherally or seemed to be along what appeared to be sinus tracts. It was either acute or subacute in type, consisting mostly of polymorphonuclear leukocytes and some lymphocytes, and mononuclear cells. Evidence of hemorrhage also was frequently present. The inflammatory reaction involved much of the perichondrium in those cases in which perichondrium was present. More often than not, no remnant of perichondrium was seen. Adjacent to this reaction were

portions of cartilage, which did not show the characteristic normal blue when stained with hematoxylin and eosin, although no attempt to control the pH of the fixing solutions was made. In this region, there were few lacunae and those present rarely contained normal nuclei. This cystic appearance gradually decreased as one moved away from the involved areas (Figs. 1 and 2).

Fig. 1.

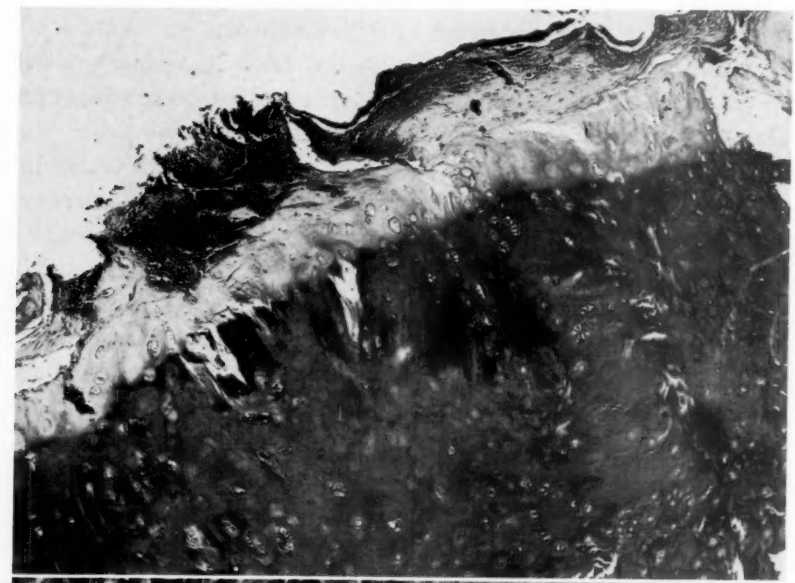

Fig. 2.

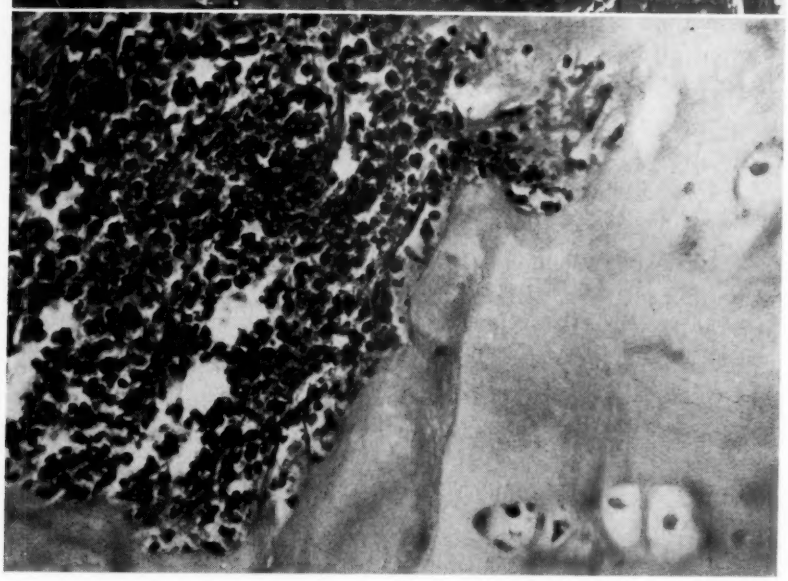

Fig. 1.—An area of costal chondritis showing the marked leukocytic reaction at the periphery of the specimen, the destruction of the perichondrium, and the underlying alteration of normal staining characteristics, paling and cystic degeneration of the cartilage (hematoxylin and eosin; ×30).

Fig. 2.—A portion of the section in Fig. 1, showing the nature of the inflammatory reaction more clearly, with a localized area of encroachment of the adjacent cartilage (hematoxylin and eosin; ×345).

COMMENT

The earlier references to this disease can be found in the German literature about the time of the turn of the century when the process was often referred to as progressive necrosis of cartilage. Röpke,[12] writing in 1908, felt that the pathologic process was primarily one of inflammation, followed by necrosis of the cartilage, and he also noted that involvement of the perichondrium was always present. This observation was seconded by Müller,[10] writing in 1911. König,[5] in discussing treatment, advocated complete excision of the cartilage because of the tendency for recurrence of the disease state in any cartilage that remained.

Martina,[8] on the other hand, felt that surgical treatment was rarely indicated and, at the same time, gave Helfrich credit for being the first exponent of radical surgery as early as 1890 in the treatment of this disease. Lampe[6] felt that the disease was due to pus and inflammation of the marrow cavity of the rib, leading to necrosis of the adjacent cartilage, and that the perichondritis was secondary to this process.

Implicated by various authors in the cause of costal chondritis were the tuberculosis and typhoid fever organisms, *E. coli,* staphylococci, senile changes in the vascularity and in the marrow itself, and various "toxic factors."

The earlier American references included an article by Murphy,[11] who wrote in 1916 on the complications of typhoid fever in general and perichondritis in particular, in which he noted the poor results with simple curettement of the draining sinuses, and recommended exposing and excising all the cartilage and a segment of the adjacent rib and sternum. Moschcowitz[9] in 1918 felt that the causative organism frequently was the tubercle bacillus initially, but that this organism was not necessarily responsible for any recurrences. He observed that at operation the cartilage was always devoid of perichondrium. He also pointed out the anatomic impossibility of removing single segments of cartilage from the sixth to the tenth rib because of their interconnections.

In the British literature in 1935 Brock[1] discussed a case of post-typhoid costal chondritis and used the term "moth-eaten" to describe the gross specimen. Chaklin,[3] in the Russian literature, expressed the opinion that the site of the original infection was the marrow cavity of the rib, except in cases of tuberculosis, and that in these cases an involved mediastinal lymph node caused destruction of the pleural surface of the adjacent perichondrium and subsequently of the cartilage.

More recently, Siler[13] cautioned against exposing cartilage in an infected wound, and Maier,[7] who echoed the vulnerability of cartilage to infection, pointed out that, when denuded of perichondrium, the cartilage undergoes necrosis and acts like a foreign body, thus producing a draining sinus. Maier included fungi as well as radical mastectomies as etiologic factors in the development of costal chondritis and seemed willing to try less radical operations in its treatment. He recommended leaving the apparently normal cartilage and covering the exposed end with viable soft tissue. Both Siler and Maier reported the possibility of an associated osteomyelitis of the sternum and of involvement of the contralateral cartilages secondary to the sternal involvement.

Brown and Trenton[2] in 1952 reported a series of cases of abscesses and sinuses that were primary in the chest wall. They stated that these lesions were often perpetuated as costal chondritis or sternal osteomyelitis, and that they were due to common blood-borne pyogenic organisms. Exceptions were noted in the cases due to tuberculosis in which the antecedent infection was thought to be an involved mediastinal node.

On reviewing our series of cases, we did not find any marked increase in the number of cases concomitant with the increase in thoracic surgical procedures, nor have we encountered any case resulting directly from the use of the thoracoabdominal incision.

The factors which have been incriminated in the etiology of the disease seem to be those which initially result in destruction of the perichondrium. It seems reasonable to assume that this loss results either in a disturbance of the growth and maintenance potential of the cartilage, or perhaps it removes a natural barrier to an infectious process. Either way, the ensuing necrotic cartilage acts like a foreign body in that it produces draining sinuses and, of course, can become secondarily infected.

The exact relationship of trauma and of radical mastectomy without subsequent radiation therapy to the development of chondritis cannot be explained satisfactorily.

It is interesting to note, however, that the concentrations of our cases in the 40-to-60-year age group corresponds to the age of onset of calcification in the costal cartilages, which Horner[4] thought to be a function of aging and an inability of the body to maintain cartilage properly.

Further analysis in 4 cases in which tuberculosis was incriminated revealed that in one patient with a draining sinus of the right anterior portion of the thorax, hemolytic streptococci were cultured from the material removed at operation, although sputum studies gave positive results for *Mycobacterium tuberculosis,* and the patient was dismissed to a sanatorium for further treatment. In a second patient who had a persistently draining sinus, both fluid in the thorax and material removed at operation, which consisted of the third left costal cartilage and the adjoining portion of sternum, were bacteriologically positive for tuberculosis. Later, because of the presence of an area of fluctuation in the scar of this same patient, all the left sixth cartilage and 2 inches of rib also were excised. A tender mass which appeared spontaneously in the region of the right breast of a third patient contained purulent material that proved to be positive for tuberculosis by guinea pig inoculation, as was material from a fourth patient with a draining sinus over the sternum, for which the cartilage of ribs four, five, six, and seven on the left was removed along with the lower sternum and 1 inch of the same cartilage on the right.

In all 4 cases, a spontaneously draining sinus developed, or was about to develop, and the origin of the pathologic process in a tuberculous mediastinal node seemed a reasonable assumption.

In regard to definitive therapy, our experience seems to parallel that of others who consider that excision of the entire cartilage in lesions located above

the level of the sixth rib usually is adequate to control the pathologic process, while lesions from about this level inferiorly probably require removal of the entire cartilaginous arch. Of course, extension into either the adjacent rib or the sternum requires more extensive surgical measures.

Review of our cases in which more than one procedure of a definitive nature was carried out revealed that in each case the pathologic process was located below the level of the fifth rib cartilage. All extensive surgical procedures were successful initially except in one case in which the entire cartilaginous arch was removed on the right and later the right fifth and sixth costal cartilages also had to be excised.

SUMMARY

A total of 17 cases of costal chondritis was gathered from the files of the Mayo Clinic. The histories were reviewed, and the gross and microscopic specimens were examined.

In addition to costal chondritis which apparently develops spontaneously and that which is secondary to pulmonary tuberculosis, there is the larger group that is related to variously located abscess cavities of the thorax or abdomen and their drainage. In our opinion this latter group is controllable, to some extent at least; therefore, a constant awareness of this condition cannot be emphasized too strongly in aiding the surgeon in his choice of incisions and in the placement of drainage tubes, and such awareness will prompt constant care in dissection in the area of the costal cartilages.

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VESICOENTERIC FISTULA FORMATION COMPLICATING DIVERTICULITIS

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INTRODUCTION

THE fact that the wall of the intestine may bear one or several outpouchings, or diverticula, has been known for many years. It is now well known that any part of the intestine may bear these pouches, but usually the condition is seen most commonly in the sigmoid colon. The presence of these pouches constitutes a condition known as diverticulosis. When these hernias become inflamed the condition is known as diverticulitis. Diverticulitis, as a disease entity, has many possible complications. It is with one of these complications (that is, the formation of a fistula between the gut and the bladder) that this paper is concerned.

HISTORY

In 1869 Klebs differentiated between true and false, as well as hereditary and acquired, diverticula. True diverticula are usually hereditary and consist histologically of all the layers of the intestinal segment from which they are derived. False diverticula are usually acquired and consist of herniations of the mucous membrane through the circular and longitudinal muscle layers. The clinical importance of diverticula was first noted by Graser in 1898, who reported a case of diverticulitis with perforation of the colon complicated by a generalized peritonitis, and it was he who determined the cause of the peritonitis, that is, perforation of several chronically inflamed diverticula.

The fact that a fistula may form in such a manner as to connect the intestine with the bladder has been known for hundreds of years. In the second century A.D. Rufus of Ephesus quoted the Greek Praxagoras as describing a case in which the patient consistently passed urine from the rectum. It was not until 1888 that Cripps wrote a treatise on the passage of air through the urethra, thereby firmly establishing vesicoenteric fistula formation as a clinical entity. By 1942 Barnes[2] collected nearly 700 cases, and since then the number reported has been markedly increased, especially because of the work of Mayo and Blunt.[4]

INCIDENCE

Diverticulosis is an extremely common condition which increases with age. Wigand[11] reported that approximately 2.5 per cent of all subjects who

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came to autopsy had diverticulosis. He based his statement on a study of 7,295 autopsies done over a 5-year period at his hospital in Germany. Some roentgenologists reported that as many as 10 per cent of all patients subjected to barium feedings and enemas have at least one diverticulum. Viable gut more easily demonstrated outpouchings than that of the cadaver, which is relaxed and more or less empty. The high incidence reported by roentgenologists is probably due to the fact that usually barium studies are performed on patients with gastrointestinal symptoms.

It is generally agreed upon by most authors that the condition of diverticulosis is most common in the sixth decade. Estimates of the average age of the patients with diverticulosis range from 54[13] to 75.[11] The disease usually is seen in some part of the large intestine, notably the sigmoid colon. Diverticulosis of the large intestine is nine times as common as it is in the small intestine, although much has been published on the diagnosis and treatment of jejunal and ileal diverticula. The incidence of this condition in men and women is approximately the same. Vesicoenteric fistula formation is considered by some to be a rather common complication of diverticulitis. Mayo and Blunt[4] studied some 202 cases of proved diverticulitis at the Mayo Clinic and found 46 (22.8 per cent) to be complicated by fistula formation.

Other investigators, notably Gouverneur, Soupalt, and Latifi,[14] investigated 324 cases of proved diverticulitis, and found only 38 (11.1 per cent) complicated by fistula formation. The incidence of fistula formation is much higher in men than in women, because in the woman the uterus acts as a barrier and infection of the adnexa must occur before the bladder can be involved. According to Mayo and Blunt[4] the average age of patients with vesicoenteric fistula is 52.

PATHOLOGY

Diverticulosis is a condition brought about by the herniation of the intestinal mucosa through the muscle layers. This outpouching usually occurs at a point of weakening of the bowel wall, often at the entrance of a large vessel. The condition may be asymptomatic for an indefinite period of time. Sometimes, however, these diverticula become inflamed, usually as a result of fecal impaction in the sacs, and precipitate the condition we know as diverticulitis. Sedgewick[7] broke down the pathologic processes into three stages. First, he described the peridiverticular stage which is characterized roentgenologically by loss of normal bowel segmentation. The second stage is the formation of definite diverticula, and the third stage is that of inflammation and is designated as diverticulitis. He pointed out that inflammation is often secondary to inspissated and trapped fecal material within the diverticula with associated strangulation.

There are four major complications of diverticulitis in general: (1) obstruction, (2) perforation, (3) fistula formation, and (4) bleeding or hemorrhage.

Obstruction may be secondary to acute or chronic diverticulitis. In the acute stage the mucosa may become extremely edematous and partially obstruct the bowel lumen, a condition which usually subsides, and almost never

requires surgery. Chronic diverticulitis may give rise to extensive fibrosis and inflammatory tumors which may completely obstruct the bowel and necessitate surgical intervention.

Perforation may take one of two forms: (a) either spreading peritonitis or (b) formation of a localized abscess. Both complications require operation. They give the clinical picture of an acute abdominal crisis, but very often the etiology of the pathologic process is very obscure until exploration of the abdomen is undertaken.

Diverticulitis is not the only cause of vesicoenteric fistula. Indeed, Ormond[6] pointed out that carcinoma, usually of the sigmoid, but sometimes of the bladder, may give rise to fistula. He stated that the reason inflammatory fistula is reported more often in the literature is because carcinomatous fistulas are not considered very interesting or important, and therefore are not documented.

Most fistulas occur in the sigmoid and the rectum, but a few are found in the ileum or cecum. The fistula may be a simple tube which allows the passage of material in both directions or it may be valvelike in type and allow passage only from bowel to bladder. A valvelike fistula may lead to cystitis and may further result in pyelitis or even an ascending pyelonephritis. If the condition of the fistula is such that urine is excreted via the rectum, the psychologic impact upon the patient is very great since the patient, having no control over urination, is reduced to the diaper state. Cystitis may be caused by any one of a number of organisms, the most common of which are *Escherichia coli, Aerobacter aerogenes,* and *Coccobacillus vesicae.* Other diseases frequently associated with vesicoenteric fistula are sigmoidocutaneous fistulas, ileosigmoidal fistulas, and occasionally carcinoma of the sigmoid. The concensus of opinion in the medical literature, however, is that carcinoma has little or no relationship to diverticulitis. In fact, some authors feel that the incidence of carcinoma of the bowel is lower in patients with diverticulitis than it is in patients without it, and that diverticulitis may have an inhibitory action on bowel cancer.

Other less common causes for vesicoenteric fistula formation do exist, and of these the most important are trauma and congenital defects.

Other complications of diverticulitis include chronic mesenteritis of the sigmoid loop, metastatic suppuration, and perforation of a diverticulum into a hernial sac, gangrenous inflammation, and formation of adhesions.

PATHOGENESIS

Most writers are generally agreed upon the etiology of diverticulosis. Constant constipation with continued straining at stool associated with a congenital weakness of the circular and/or longitudinal muscle layers favors the development of diverticula. Both of these factors need not necessarily be present, for the condition may exist in the total absence of one, but not both of them. Most cases seem to represent a combination of the two. Other factors which contribute to the condition are obesity and persistent passing of flatus.

SYMPTOMS AND SIGNS

The clinical picture of acute diverticulitis closely resembles that of acute appendicitis except for the fact that the complaints are referable to the left side of the abdomen. The pain is usually localized in the left lower quadrant and is cramping and intermittent in quality. It may however, extend to involve the entire abdomen, or even the back.

The pain is often relieved by a bowel movement. Nausea, vomiting, and a change in bowel habits (either constipation or diarrhea) are often frequent complaints. The patient may be in a state of chronic constipation, interrupted by occasional diarrhea. There is also fever, leukocytosis, and an increased sedimentation rate.

Sometimes a tender mass may be palpated in the left iliac fossa, which may be a diverticulum impacted with feces, or an inflammatory tumor. Often it is difficult, even at operation, to distinguish this inflamed mass from a carcinoma of the bowel. Bloody and tarry stools are uncommon.

If an acute attack of diverticulitis goes on to formation of adhesions and subsequently of a fistula, the symptoms and signs become very striking. In most cases the complaints are chiefly referable to the urinary tract. Urinary urgency, frequency, and dysuria appear early, probably even before the development of the fistulous tract is completed. Once the fistula becomes patent, pneumaturia appears, usually accompanied by hematuria. Pneumaturia is regarded by many to be pathognomonic of the condition, but Mayo and Miller[5] pointed out that there are other conditions which may bring about pneumaturia. They included pneumaturia in cases of diabetes due to yeasts fermenting urine containing sugar, in chronic infections of the renal pelvis or urinary bladder by gas-forming organisms, and in a patient into whom air has been introduced by catheterization. The pneumaturia usually occurs at the end of urination. Fecal particles in the urine (fecaluria) are diagnostic of the condition. The foul-smelling sediment gives a rapid clue to the presence of a fistula. Usually urinary pain and frequency are so dominant in the mind of the patient that he rarely mentions the pneumaturia while describing his symptoms. Typically, the patient tells of feeling as though something had broken, and then observing blood in the urine. Once pneumaturia begins, pain follows in about 2 weeks, and fecaluria about 3 weeks later. Since infection is present, chills and fever are often experienced, and since the condition arises from diverticulitis the symptoms of that condition will be present. These symptoms may not necessarily be acute, and Mayo and Blunt reported one case in which the patient had been experiencing pneumaturia and fecaluria intermittently for 8 years. The condition is also accompanied by suprapubic, perineal, or genital pain. The pain is probably due to one or more of the following factors: the inflammatory process accompanying fistula formation, engorgement of the fistulous tract by solid material, and trauma associated with passage of solid material through the fistula.

DIAGNOSIS

The diagnosis is made by (1) the history, (2) sigmoidoscopy, (3) cystoscopy, or (4) x-ray study.

The history may be vague and nonspecific. Most authors claim that the vast majority of patients with vesicoenteric fistulas of this type state that they have been receiving treatment from their local physicians for urinary tract disease. On the other hand, the history may be so specific that the diagnosis is easily established.

Sigmoidoscopy is the least reliable method of diagnosis for both diverticulitis and the ensuing fistula formation. Mayo and Blunt stated that sigmoidoscopy was negative in one-half of the known cases of vesicointestinal fistula examined. It was noncontributory in the 3 cases reported in this paper. Occasionally, the mouth of the fistula in the sigmoid can be visualized, but this finding is the exception rather than the rule. If the case is simply uncomplicated diverticulitis, the mouth of the diverticulum can often be visualized after the acute attack has subsided.

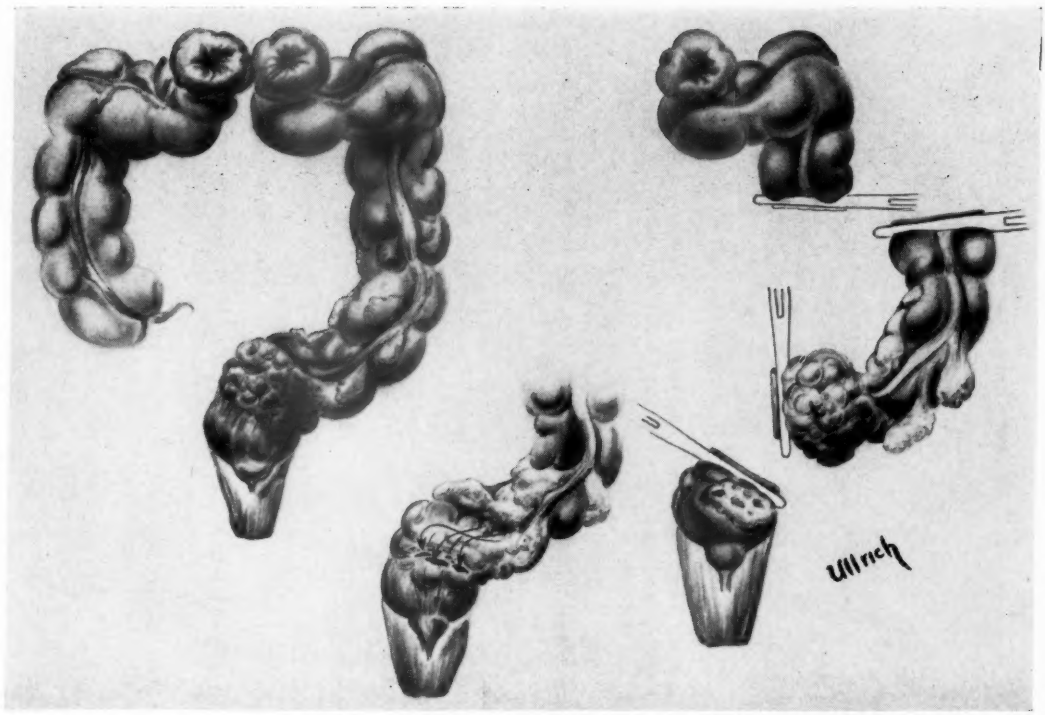
Cystoscopy remains one of the best diagnostic methods. According to Barnes[2] the fistulous opening itself is rarely seen, but the bladder mucosa around the opening has a characteristically inflamed appearance, from which the diagnosis may be made. This method gives a high percentage of positive results.

Roentgenology also provides a valuable diagnostic tool. Barium feedings and barium enemas often outline the fistulous tract. Often barium particles can be observed in the bladder after enema, thus affording a positive diagnosis. This method however is not as reliable as simple cystoscopy. For diverticulosis and diverticulitis, however, x-ray remains the most reliable tool, especially if the condition is quiescent. The diverticula are clearly outlined and are readily seen on administration of a barium enema. Wigh and Swenson[12] stress the point that x-ray is not infallible for often there is obstruction to the retrograde flow of the barium. Although a positive diagnosis is not always possible, x-ray can rule out the absence of diverticulitis and thus exclude it as a source of left lower quadrant pain.

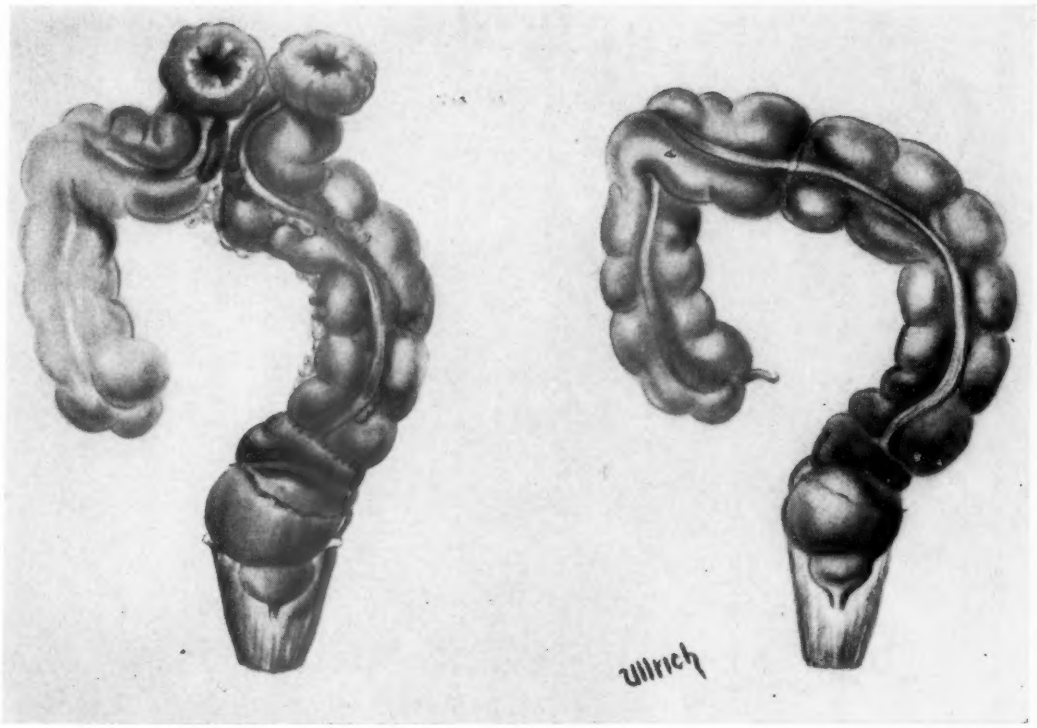
TREATMENT

Diverticulitis is generally regarded as a medical problem, while fistula formation complicating diverticulitis is always dealt with surgically. Many feel however that diverticulitis should be treated surgically. Babington[1] pointed out that in many cases purely medical treatment is insufficient and when these cases are operated upon after prolonged conservative treatment the postoperative mortality is quite high.

Mayo and Blunt outlined the surgical procedure for dealing with vesicoenteric fistula. First, there is the preoperative administration of antibiotics to rid the gut of its flora. Second, laxatives, enemas, and low residue diets,



A.



B.

Fig. 1.—*A*, Left drawing shows involvement of sigmoid and diverting type of loop colostomy that is carried out; center, course of feces from sigmoid into urinary bladder; right, resection of sigmoid in second stage of procedure. *B*, Left shows primary anastomosis of sigmoid in second stage; right, closure of colostomy in the third stage.

TABLE I. STUDY OF THREE PATIENTS

	MR. L. K.*	MRS. M. C.	MRS. W. F.
Age	46	60	66
Date of admission to hospital	December, 1950	September, 1953	May, 1950
Chief complaint	Severe left lower abdominal pain with frequent desire to defecate but inability to do so. Relieved by rest and inactivity	Abdominal cramps, bloody rectal discharge and hematuria	Intermittent abdominal cramps of 2 days' duration
Duration of complaints	1½ days	3 weeks	2 days
Past history	Constipation for several months requiring mild cathartics	For previous 3 to 4 years, frequent episodes of abdominal cramps in left lower quadrant, rectal bleeding, hematuria, nausea and vomiting, diarrhea (often bloody)	Irrelevant
Other complaints	Vomiting of 2 days' duration	Explosive defecation precipitated by eating	Constipation, anorexia, and difficult voiding
Laboratory findings	W.B.C. 14,000	W.B.C. 21,000	W.B.C. 17,000
Physical examination	Tenderness with rebound tenderness in both lower quadrants, descending colon palpable	Tenderness with rebound tenderness left lower quadrant, with a questionable palpable mass in the abdominal left lower quadrant	Spasticity lower quadrant of abdomen. Tenderness to right of midline below umbilicus and in suprapubic region. Hypoactive peristalsis. Tenderness in right pararectal area on rectal examination
First operation	Drainage of abdominal abscess left lower quadrant	Transverse colostomy	Appendectomy. At operation it was noted that rectosigmoid was infected and adherent to urinary bladder
Complications	On the fourteenth postoperative day pneumaturia and fecaluria	Difficulty controlling pre-existing diabetes mellitus	One month later pneumaturia, chills, nausea and vomiting
X-ray findings	Multiple diverticulitis with narrowing of the rectosigmoid junction	Low-grade obstruction in rectosigmoid area due to diverticulitis or tumor	Some tubular narrowing of rectosigmoid with multiple diverticulitis
Cystoscopy	Marked infection noted in the left fundal portion of the urinary bladder	Three small apertures with marked secondary infection in left fundal area of urinary bladder	Landmarks obscured by marked cystitis. Indigo carmine instilled in urinary bladder, recovered from rectal washings

Sigmoidoscopy	Obstruction total and regional of 7 inches, some diverticula noted	Narrowing at a level of 6 to 7 inches	Diverticula with narrowing of rectal canal at 6 to 7 inches above anal verge
Second operation	Transverse colostomy 17 days after incision and drainage of abscess	Resection of sigmoid with primary anastomosis of sigmoid 4 months after transverse colostomy	Transverse colostomy 1½ months after appendectomy
Third operation	Resection of sigmoid with end-to-end anastomosis 5 months later	Closure of colostomy 3 months after primary anastomosis	Resection of rectosigmoid 4 months after colostomy. Catheterized left ureter prior to operation
Surgical repair of urinary bladder	Not necessary	Not necessary	Closure of opening in urinary bladder
Fourth operation	Closure of colostomy 2 months after anastomosis of sigmoid	None	Closure of colostomy 3 weeks after primary anastomosis of sigmoid
Postoperative x-rays	Slight narrowing in the region of the sigmoid junction	Slight narrowing in the region of the sigmoid junction	Slight narrowing in the region of the sigmoid junction
End results	Excellent	Excellent except for chronic constipation	Excellent

*We are indebted to Dr. John Spellman for allowing us to publish his material on this patient.

fluids and electrolytes, and blood if necessary are administered. The operation is usually performed in two stages (Fig. 1). First, a preliminary colostomy is done to divert the fecal stream proximal to the vesicosigmoidal fistula. This sidetracking permits the inflammatory reaction around the fistula to subside. The next stage involves some sort of resection, the type of which is up to the surgeon. He may do an anterior resection with an end-to-end anastomosis, or an extraperitoneal resection with a catheter colostomy in the proximal barrel.

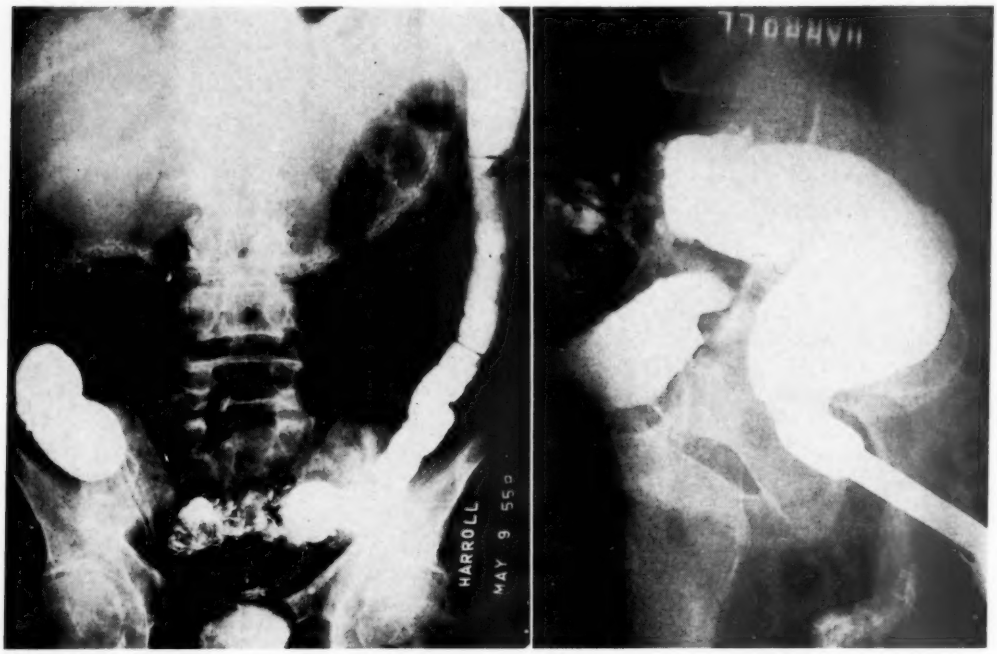


Fig. 2. Fig. 3.

Fig. 2.—Anteroposterior view of barium enema demonstrating spillage of barium from sigmoid via fistulous tract into the bladder.

Fig. 3.—Lateral view of barium enema demonstrating spillage of barium from sigmoid via fistulous tract into the bladder.

When the sigmoidectomy is performed, the opening in the bladder is repaired when the sigmoid segment is exteriorized. When an anterior resection is performed, the opening in the bladder is repaired simultaneously.

The fistulous tract should be dissected free from the bladder wall, leaving a clean surface. The bladder is then closed in layers with No. 1 chromic catgut.

Best results have been obtained by using suprapubic drainage until the the wound is completely healed.

Table I reports in comparative columns the results in 3 patients successfully treated for sigmoidovesical fistulas.

It is obvious from the Table that the patients were in the older age group. All of the major complications were referable to the lower abdominal wall, and there was some change in bowel habits. In 2 of the 3 cases reported.

there was strong evidence of long-standing change in bowel habits. The difficulty in exact diagnosis is obvious in that one patient was thought to have acute appendicitis and another was thought to have an abdominal abscess of questionable etiology. The concomitant urinary infection that accompanies this condition is obvious. Barium enema and sigmoidoscopic findings are significant as adjuncts to correct diagnosis. Cystoscopic examination will reveal either the actual fistulous openings or severe infection. It is interesting to note that in one patient indigo carmine instilled in the bladder could be recovered from rectal washings. Two of the 3 patients did not require surgical repair of the urinary bladder. In each instance the postoperative films demonstrated narrowing of the rectosigmoid junction.

The extreme technical hazards encountered in the actual resection and anastomosis of the diseased bowel should be emphasized. Inlying ureteral catheters are of some value. Undoubtedly in the past many patients with this condition have been subjected inadvertently to Miles abdominoperineal resection.

The rarity of this condition is evidenced by the fact that at the Massachusetts General Hospital only 11 cases have been found up to the present date.[10]

Figs. 2 and 3, showing preoperative x-rays of the barium enema in the case of Mrs. M. C. in Table I, are most dramatic.

SUMMARY

1. There has been presented the etiologic factors, treatment, and complications of vesicoenteric fistulas accompanying diverticulitis.

2. There has been outlined the step-by-step procedure of the treatment of vesicoenteric fistulas.

3. Three cases reported with successful end results have been described.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

NEONATAL ASPHYXIA PALLIDA TREATED WITH HYPOTHERMIA ALONE OR WITH HYPOTHERMIA AND TRANSFUSION OF OXYGENATED BLOOD

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RESULTS with experimental animals (guinea pigs, rabbits, and puppies) have shown that reduction of colonic temperature is very effective in preventing death from experimental asphyxia with 95 per cent N_2 plus 5 per cent CO_2.[5-8, 13] Even in guinea pigs, which at birth behave much more like adults than babies, a 10° C. reduction in body temperature will completely protect 100 per cent of the animals from an exposure which is lethal for 100 per cent of the control littermates.[8, 13] On the other hand, premature humans not only tolerate low body temperatures, but under certain circumstances at least, live longer when cool than when at normal temperature. Nonviable apneic premature humans can be maintained for 12 hours or more with perfusion of oxygenated blood if kept at 25° C. body temperature, whereas their hearts stop within 60 to 90 minutes if they are kept at 37° C.[2] One 580 gram infant was maintained for 21 hours at temperatures below 22° C. During this time it was cooled to less than 4° C. on five separate occasions. Its temperature reached 0.1° C. during the last two episodes. This temperature produced asystole, but cardiac contractions recommenced spontaneously upon rewarming.[11] In addition, in experimental animals hypothermia has been found to potentiate the beneficial effects of injected Nembutal, nucleotide, and hydrogen peroxide.[8] Thus the time appeared ripe for a clinical trial of hypothermia as an adjunct to other resuscitative measures for asphyxia neonatorum.

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MATERIAL AND METHODS

Six babies for whom other methods of resuscitation had proved ineffective were placed on their backs in running cold tapwater (8° to 14° C.) and were cooled until their deep colonic temperatures had fallen to 23° to 30.4° C. The periods of apnea ranged from 14 to 79 minutes. All infants reached the asphyxia pallida stage with no muscle tonus and with pulseless precordium, and one baby underwent a 4-minute period of asystole. In 3 infants regular breathing began spontaneously during cooling without further treatment. The other 3 received transfusions of 75 to 150 ml. of oxygenated blood in addition. Rewarming was gentle. It required from 7 to 50 hours for the babies' temperatures to attain 35° C. Electrocardiograms were recorded on an Elema Triplex apparatus beginning at the time the lowest body temperature was reached and during the period of rewarming. Blood pressure records were made by means of a catheter introduced into the internal iliac artery and connected with a strain gauge (Elema electromanometer). Electroencephalograms were made at the Pediatric Clinic, Karolinska Sjukhuset, Stockholm, and were read by Dr. Marcel d'Avignon. A 6-channel Graff electroencephalograph was used and bipolar records were taken with 14 silver electrodes. Auditory tests were performed according to the techniques of Wedenberg[19] and included (1) threshold determinations of the aureopalpebral reflex and (2) threshold determinations of intensity necessary to awaken the child from sound sleep. Details of these tests and an account of postnatal care will appear elsewhere.[21]

RESULTS

All 6 babies were resuscitated: three with the aid of hypothermia alone and three with hypothermia combined with transfusion of oxygenated blood.

TABLE I

CASE	SEX	WEIGHT (GM.)	COMPLICATIONS	CONDITION AT BIRTH	GASPS BEFORE COOLING
1	M	3,290	Eclampsia; general anesthesia → respiratory depression	Pink → cyanotic → pale and atonic	None
2	F	3,000	Toxemia; general anesthesia for imminent asphyxia	Atonic and pale → pallid	1 at 1 min.
3	M	2,790	Long labor (28 hr.)	Cyanotic → pale and atonic	3 in first min.
4	M	3,500	4 weeks postmature; long labor (47 hr.)	Grayish blue → atonic and pale	None
5	F	3,700	Pelvic anomalies requiring cesarean section; general anesthesia; mother cyanotic	Grayish blue → atonic and pallid	None
6	M	3,500	2 weeks postmature; 41-hr. labor; oversedation (?)	Grayish blue → atonic and pale	2 in 3 min.

Table I summarizes briefly the conditions immediately preceding and following birth of the 6 babies. Birth was complicated in the first case by convulsions in the mother due to eclampsia which necessitated delivery under general anesthesia. Since, as shown by Snyder and Rosenfeld,[18] sedatives depress the fetal respiratory center before they influence that of the mother, it appears probable that apnea was caused in this infant by depression of the respiratory center by the anesthetics used. The baby was pink at birth indicating that no asphyxia was present until after delivery. It passed through asphyxia livida to asphyxia pallida during the 15 minutes when conventional resuscitative measures were employed. During this period it failed to produce even a single respiratory movement.

The second case was complicated by toxemia of pregnancy with elevated blood pressure and nonprotein nitrogen. Delivery was completed with the aid of mid-high forceps and general anesthesia when imminent asphyxia of the baby threatened. The baby was pale and atonic when delivered and achieved only one weak gasp.

Delivery of the third baby was preceded by a long labor, but no signs of imminent asphyxia were noted during the 28 hours between the onset of labor and delivery of the child. However, at birth the infant was cyanotic, and after only three weak respiratory movements rapidly became pale and atonic.

The fourth case, a 4 weeks postmature male infant, was delivered after a long labor of 47 hours complicated by threatened asphyxia in utero. It was in poor condition at birth with grayish-blue skin, no muscle tonus, pulseless precordium and slow heart. Conventional resuscitative efforts failed to produce a single gasp.

The delivery of Case 5 was complicated by pelvic anomalies which necessitated a cesarean section. Respiratory complications developed in the mother during the operation and she had slight cutaneous cyanosis in spite of treatment with 100 per cent O_2. At birth the baby was in very bad condition with skin grayish blue, no muscle tonus, and a weak slow pulse. No respiratory movements could be elicited until after it was placed in the cold water.

Complications in the sixth case were 2 weeks postmaturity and a cervical spasm which produced a 41-hour labor and the mother required general anesthesia for the final delivery. At birth the infant was grayish blue and atonic. After two weak gasps during the first 3 minutes it resisted all efforts to get its respiratory cycle started.

Table II summarizes the cooling records in the 6 cases. Water temperatures were between 8° and 14° C. Cooling was begun between 4 and 15 minutes after birth and continued for 4 to 39 minutes. The minimal temperatures were between 30.4° (Case 3) and 23° C. (Case 4). Three babies gasped one or more times during cooling (Cases 2, 5, and 6); the rest began breathing without any preliminary gasps.

TABLE II. COOLING RECORDS

CASE	COOLING				MINIMUM COLONIC TEMPERATURE	GASPS DURING COOLING
	WATER TEMPERATURE	BEGUN AT	ENDED AT	TOTAL TIME		
1	8° C.	15′	32′	17′	25° C.	None
2	12° C.	6′	16′	10′	28° C.	1 at 10′ 1 at 12′
3	12° C.	8′	12′	4′	30.4° C.	None
4	14° C.	8′	47′	39′	23° C.	None
5	12.5° C.	4′	15′	11′	25° C.	1 at 4′
6	10° C.	8′	22′	14′	25.1° C.	2 to 4 per min.

From Table III it may be seen that in Cases 1, 2, and 3 regular respiration began spontaneously without further treatment while the babies were being cooled. Prior to this the color of the skin had changed in each case from ashen gray through blue to pink with a concomitant increase in muscle tonus. This was evidence that circulation was improving and that the blood was picking up oxygen in the gastrointestinal canal where it had been injected during the resuscitation attempts which had preceded the cooling. The rapid recovery of brain function was indicated by the time and temperature at which the first cry was given in these first 3 cases (within 3 minutes of breathing).

TABLE III

CASE	BLOOD TRANSFUSION	BEGINNING OF RESPIRATION		FIRST CRY	
		TIME	TEMPERATURE	TIME	TEMPERATURE
1	None	23′	27° C.	40′	25° C.
2	None	15′	32° C.	15′	32° C.
3	None	14′	34° C.	17′	33° C.
4	150 ml. at 76′ to 80′	79′	23° C.	105′	23° C.
5	100 ml. at 16′ to 25′	18′	32° C.	19′	31° C.
6	75 ml. at 38′ to 47′	52′	25° C.	67′	25° C.

In Cases 4, 5, and 6 transfusions of 75 to 150 ml. of oxygenated blood were given when it appeared that hypothermia alone would not be adequate. In each case, heparinized Rh-negative blood with low anti-A and anti-B titers and lacking in α and β hemolysins was used. For intracardiac injections it is essential to use heparinized blood. Work on nonviable prematures has shown that citrated blood damages the heart by binding the calcium.[2, 16, 20]

The baby of Case 4 was born in bad condition, with atonic muscles, pulseless precordium and umbilical cord, and slow heart rate. He failed to respond to routine methods of resuscitation including gastrointestinal oxygen. Cooling, begun after 8 minutes, produced only slight improvement in the color and no improvement in muscle tonus or heart action. After 1 hour and 16 minutes no heartbeat could be auscultated and the infant appeared clinically dead. At this point an attempt was made to resuscitate the infant by a blood transfusion. Experience with nonviable premature infants had shown that transfusions through the umbilical vein are ineffective when the cardiac contractions are too weak to propel the blood. However, if a retrograde transfusion

is made through the umbilical artery, the heart can often be revived.[2, 16, 20] For this reason the patient in Case 4 was transfused through an umbilical artery. During 4 minutes he received 150 ml. of blood, and before the end of the transfusion he was breathing regularly. Twenty-five minutes after the end of the transfusion, with the temperature still at 23° C., the infant cried upon stimulation. As will be discussed later, this infant had three episodes of hematemesis at 21, 22, and 30 hours of age and died, but the autopsy did not establish any connection between the long period of asphyxia and the pathologic findings.

Case 5 was delivered in very poor condition by abdominal cesarean section after 13 hours of unsuccessful labor because of pelvic anomalies. Nitrous oxide, ether, and oxygen were administered as anesthesia. Because of respiratory complications the mother showed a slight cutaneous cyanosis during the operation in spite of intermittent administration of 100 per cent oxygen. At birth the infant had a grayish-blue color, with no muscle tonus and slow feeble pulse in the umbilical cord. For the first 4 minutes the condition deteriorated in spite of resuscitative measures. At this time the baby was placed in 12.5° C. water for 11 minutes. Although she gave one gasp and the skin color improved, muscle tone and heart rate did not improve. Therefore, 16 minutes after birth an intravenous transfusion of 100 ml. of oxygenated blood was started. Two minutes later, at a body temperature of 32° C., regular spontaneous breathing began and one minute after that the infant cried. The infant vomited at 26 hours after birth and subsequently developed respiratory distress with slight cutaneous cyanosis. Rectal temperature was lowered from 36° to 30.6° C. by a 3-minute exposure to water at 12.5° C. and tracheobronchial aspiration was performed. This relieved the respiratory distress and the second rewarming began at 27 hours with the infant in good condition. No further attacks of cyanosis occurred.

The last infant was delivered under general anesthesia with the aid of a vacuum extractor 41 hours after the onset of labor because of slowing of the fetal heart during uterine contractions. The infant was atonic and skin color soon became grayish blue. He gave two gasps in the first 3 minutes and his condition deteriorated in spite of resuscitative measures. Eight minutes after birth he was placed in water at 10° C. for a 14-minute period. During cooling the skin gradually became pink but muscle tonus did not increase. Six minutes after the beginning of cooling the infant began to gasp at 15- to 30-second intervals. After he was removed from the cooling bath, gasping decreased to 1 per minute. Accordingly, a transfusion of 75 ml. of blood was given between the thirty-eighth and forty-seventh minutes. This resulted in an increase in muscle tonus, but the infant continued to gasp. A large amount of mucus was aspirated from the trachea 52 minutes after birth. This was immediately followed by normal respiration at a rate of 32 per minute. The remainder of the history was uneventful up to the nineteenth day when he was sent home in good condition.

Table IV summarizes briefly the time required for the temperatures to rise to 35° C., the results of the auditory tests, and the subsequent history to date. In the immediate postpartum period the temperatures of normal babies fall to approximately 35° C. (Fig. 1).[21] For this reason no attempt was made to rewarm these 6 babies beyond that point. By the second or third day, however, the body temperatures of 5 had reached the vicinity of 37° C. It is to be noted that Case 6 did not reach 35° C. until 2 days after birth. This baby was kept naked in a room at 26.6° C. for 6 hours. Subsequently it was covered with woolen blankets, but at no time was there active heating. This baby showed no unfavorable reactions to the treatment.

TABLE IV

CASE	REWARMED TO 35° C. IN	HEARING TESTS		SUBSEQUENT HISTORY
		AGE	RESULTS	
1	6+ hr.	22 days	Normal	6,550 Gm. at 6 mo.
2	20 hr.	24 hr.	Normal	4,200 Gm. at 58 days
3	8 hr.	15 hr.	Normal	3,970 Gm. at 63 days
4	17 hr.	12½ hr.	Normal	Died at 30½ hr.; aspired vomitus
5	8+ hr.	30 hr.	Normal	Respiratory distress at 30 hr.; cooled to 30.6° C., recovered; 4,650 Gm. at 67 days
6	50 hr.	20 days	Normal	3,590 Gm. at 17 days

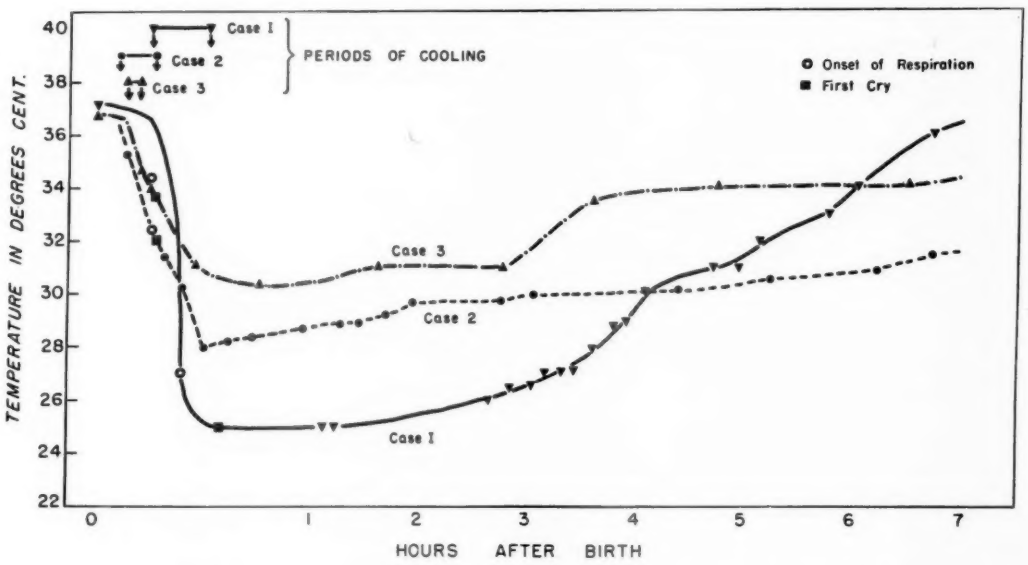

Fig. 1.—Records of Cases 1, 2, and 3 showing periods of cooling and time and temperature of the onset of breathing and first cry.

The results of the ECG, EEG, hearing and blood chemistry studies will be reported in detail elsewhere.[21] In general it may be said that no significant deviations from normal were noted after return to normal body temperature. The results of the hearing tests are summarized in Table IV because of the importance of these findings. All 6 infants, including the one which was apneic for 79 minutes, gave normal responses. These tests (performed by E.

W.), which covered the frequency range from 500 to 4,000 cycles per second, showed normal sensitivity even at the highest frequencies. This is in sharp contrast with the records of infants recovering from severe asphyxia with neurologic defects and also with many infants who recover from asphyxia without patent neurologic damage. Fig. 3 illustrates hearing tests on the patient in Case 4, on one infant that recovered from asphyxia without the

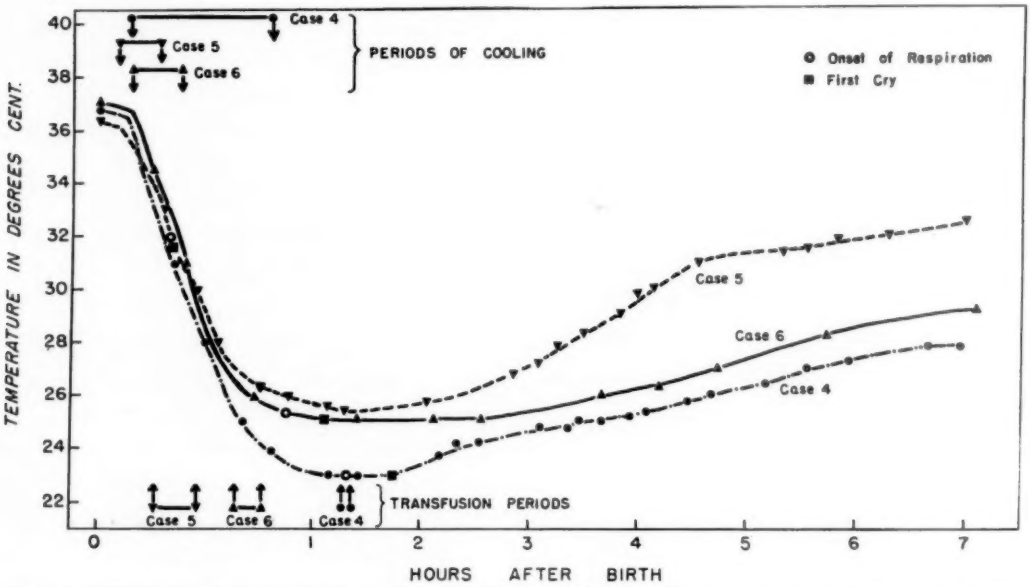

Fig. 2.—Records of Cases 4, 5, and 6 showing periods of cooling and transfusion of oxygenated blood and the time and temperature of onset of breathing and first cry.

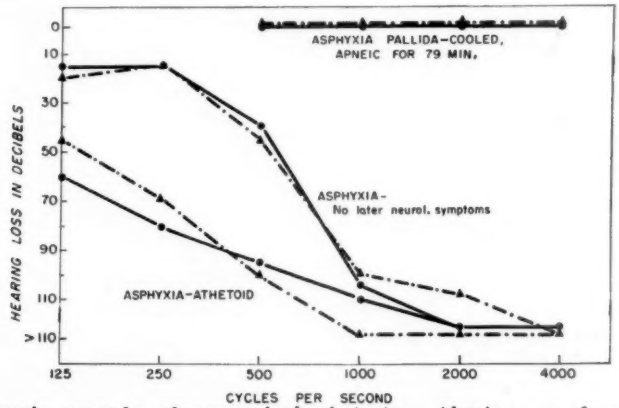

Fig. 3.—Sample records of auropalpebral tests. Abscissa = frequency in cycles per second. Ordinate = hearing loss in decibels from 0 to 110. The lowest point indicates loss greater than 110 decibels. No tests were made at greater sound intensity.

aid of hypothermia and showed no neurologic symptoms, and on one infant that developed athetosis following recovery from asphyxia neonatorum. It is to be noted that although the latter 2 babies showed loss of acuity for all frequencies, it was the tones of highest frequency which were the most sensitive to asphyxia. None of the 6 babies which were treated for asphyxia by cooling showed any impairment of sensitivity even at 4,000 cycles per second.

The right-hand column of Table IV shows that since their discharge from the obstetrics department the babies have been increasing in weight. They appear healthy and thus far have shown no signs of neurologic damage. Only time can tell whether there may be occult conditions which may become visible later. This possibility must not be overlooked since it actually occurred in a rhesus monkey asphyxiated experimentally (at normal body temperature) at 9 days of age. Behavioral changes and reduced ability to learn were not discovered until it was separated from its mother at one year of age.[15]

DISCUSSION

These 6 cases of asphyxia neonatorum treated with hypothermia bring the human infant into line with other newborn mammals in which cooling has been demonstrated to be a lifesaving procedure.[8] The original rationale for its use is the very well-known principle of physics and chemistry, Van't Hoff's law, which states that the rates of chemical reactions vary with the temperature. Thus, by reducing the rate of consumption of energy stores, it was postulated that drastic cooling would greatly prolong asphyxial survival.[5]

Earlier methods, involving the alternate use of cold and hot water were based upon the belief that respiration can be initiated by shocking the nervous system by sudden changes in temperature. This may be effective in slightly or mildly asphyxiated infants; however, by the time muscle tonus is lost central nervous system depression is so great that the infant is incapable of responding to any stimulus. The same situation explains the ineffectiveness of pharmacologic respiratory stimulants in severe asphyxia. By way of contrast, it is to be noted that in all of these asphyxia pallida cases reduction of body temperature produced a noticeable improvement and in three no other treatment was needed to produce complete recovery.

A secondary effect of hypothermia is generalized vasoconstriction.[9] In asphyxia pallida the baby is in a shocklike state with generalized vasodilatation which results in pooling of the blood and a totally inadequate circulating blood volume. The early appearance of normal breathing in the first 3 cases suggests that some sudden response to the cold water may have taken place. The intrinsic muscles of the blood vessels may react to cold even in the absence of nervous stimulation. An example of this was reported for the isolated dog aorta.

Furthermore, temperatures in the range here reported have been shown to increase the vigor of contraction of heart muscle and the stroke volume (Fig. 2).[17] This may, in fact, have been the point in Cases 1, 2, and 3 where the break in the vicious cycle of asphyxia → apnea → more severe asphyxia took place. Oxygen introduced into the gastrointestinal tract saturates the hemoglobin of the red blood cells in the capillaries as indicated by their bright red color. With increased venous return made possible by vasoconstriction, only a few vigorous heartbeats would be required to improve greatly the

oxygenation of the blood in the coronary arteries. This would increase both the rate and stroke volume and thereby initiate a chain reaction leading to the beginning of spontaneous respiration.

In the last 3 cases hypothermia alone proved able to prevent death but was unable to initiate breathing. In two of these a transfusion of oxygenated blood was sufficient to do so. In the last case true breathing did not begin until the excessive secretions were removed from the tracheobronchial tree. In Case 5 the oxygenated blood was delivered to the right atrium via the umbilical vein and in only 2 minutes produced the desired results—regular breathing. It is to be noted that intra-arterial transfusion was used in Case 4. The heart of this infant had actually been in asystole for about 4 minutes when the transfusion was started. Intravenous transfusions when the heart is in extremis have proved ineffective in experiments on previable premature infants.[2] On the other hand, retrograde transfusions through an umbilical artery often revive hearts which have previously failed to react to a similar intravenous transfusion. Recently a suggestion has been offered to explain why intravenous transfusions at this stage appear to hasten rather than postpone cardiac standstill.[16] In the flabby, agonal heart an intravenous injection dilates the right atrium and ventricle. This dilatation compresses the coronary sinus and its tributaries, thus impeding rather than increasing coronary flow. The fetus, with its patent foramen ovale, offers the possibility of filling the left atrium and ventricle in intravenous transfusions as a result of transatrial flow. However, as shown by Windle and Becker,[22] thorough mixing of the blood in the right atrium occurs when circulation is poor. In addition, injections into the umbilical vein of stillborn fetuses have been found to fill the liver first and then to pass in reverse direction into the portal vein, inferior vena cava, and superior vena cava.[16] Thus, when circulation has actually ceased (as in Case 4), intraveous transfusions fail to deliver the oxygenated blood to the required location. On the contrary, retrograde arterial transfusion circulates the oxygenated blood through the coronary system directly. Since the aortic valves close effectively against back pressure even in the dead heart, coronary flow is assured in retrograde transfusions.

The finding that all 6 babies had normal auditory acuity even for sound in the 4,000 cycles per second range is of great importance. These objective measurements provide a partial answer to the question which is constantly asked as to whether newborn organisms which recover from asphyxia with the aid of hypothermia actually retain their mental faculties. Studies indicate that the parts of the auditory pathways which are most sensitive to anoxic damage are the dorsal cochlear nuclei.[3] Tones of highest frequency are carried to these nuclei[4] and recent investigations[1] suggest that the conditions in the dorsal cochlear nuclei provide a good index of the presence or absence of damage to the brain as a whole.

It is of some importance that the exposure to asphyxia was preceded by a different history in each of these 6 infants. This suggests that there is a broad spectrum of cases in which cooling may be expected to be efficacious.

From theoretic considerations hypothermia should be beneficial in all situations in which severe hypoxia or asphyxia are complicating factors because of the fundamental nature of its effects—reduction of the basic metabolic requirements of all tissues.

Case 1 is of special interest since it provides clinical confirmation of the fact, established for newborn guinea pigs, that hypothermia is effective in protecting narcotized babies from asphyxia. Because in itself it depresses metabolism, narcosis prolongs asphyxial survival slightly at normal body temperature. However, if narcotized animals are cooled to 20° C. or less and asphyxiated, there is a striking increase in survival time over that of littermates even at the same temperature.[8]

Finally, attention is called to the combination of simplicity and effectiveness which the treatment offers. Water at about 10° C. generally is available even in home deliveries. If cold water is not available, data on animals indicate that chipped ice or circulating ice water is highly effective. In a recent study there was appreciable cooling of the brain of stillborn fetuses in 10 minutes as a result of immersion in circulating ice water. As shown by cooling rates in animals of the same size (adult guinea pigs) cooled when alive and after death, considerably faster cooling of the internal organs may be anticipated in living babies.[10] The results with cold water reported here leave little to be desired. However, there may be occasions when a more rapid method of cooling is necessary to save the life or mentality of an asphyxiated infant. Animal experiments give no indications that unfavorable reactions are to be expected from immersing asphyxiated infants in ice water. Indeed, partial asphyxiation has been found to be essential if mice are to recover completely from cooling to less than 1° C.[12, 14]

SUMMARY

1. Six babies suffering from asphyxia pallida were cooled in running water at temperatures between 8° and 14° C. The total time in the water varied between 4 and 39 minutes. The minimum colonic temperatures were 23° to 30.4° C.

2. In 3 cases regular breathing began spontaneously without further treatment 14 to 23 minutes after birth and at body temperatures of 27° to 34° C.

3. The other 3 infants were given 75 to 150 ml. of oxygenated blood when it appeared that cooling alone might not be adequate. These began breathing at 18 to 79 minutes after birth and at temperatures between 32° and 23° C.

4. Hearing tests performed between 12½ hours and 22 days demonstrated no loss of acuity between 500 and 4,000 cycles per second. This is in sharp contrast to records previously obtained from babies that had recovered from severe asphyxia with or without neurologic symptoms.

5. Electrocardiograms, electroencephalograms, blood pressure, and blood chemistry studies were made but are being reported elsewhere.[21]

6. One infant died at 30½ hours, apparently from aspiration of vomitus. The other 5 are alive, growing, and apparently normal.

7. Hypothermia has been found to be a lifesaving measure in experimentally asphyxiated newborn animals. It appears to have played the same role in these newborn human infants.

8. Recovery is possible from apneic periods of over one hour when hypothermia is combined with injections of oxygenated heparinized blood.

ADDENDUM

Since submission of this report, two additional severely asphyxiated infants have been treated successfully with hypothermia. One was delivered by cesarean section because of placenta previa totalis and malposition of the fetus. Apnea in this infant lasted 8 minutes. It was cooled to 32° C., rewarmed spontaneously in about 3 hours, and is doing well. The second infant was discovered blue and apneic by her mother after breast feeding. Approximately 17 minutes elapsed before hypothermia was induced, and by this time the baby was in very poor condition. However, it was successfully revived and subsequently responded normally to the auropalpebral reflex test.

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Editorial

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Sigmoidoscopy and Biopsy

The use of such slogans as "Sigmoidoscopy is every clinician's business," "Sigmoidoscopy does not require a proctologist," and "Proctosigmoidoscopy should be made a routine part of every physical examination" has paid dividends to the patient and the clinician. While the main purpose is to detect asymptomatic benign and malignant neoplastic lesions, this maneuver also discovers a variety of nonneoplastic, sometimes neglected, lesions. Parenthetically, the contemporary literature is full of quibbling about the incidence of these lesions, particularly polypoid adenomas, in the general population.

The advocacy of the performance of routine endoscopy by the inexpert, however, carries certain responsibilities. Clinical facilities for teaching endoscopy should be provided at the local hospital level, although many clinicians have trained themselves to perform sigmoidoscopy, and through sheer practice have acquired the necessary skill for the performance of this procedure. For teaching purposes the instrument that makes possible the simultaneous examination by two persons may be utilized advantageously. All other endoscopes should be of simple design but should provide the best illumination possible.

A disputable point is: What distance of the terminal portion of the colon should be examined "routinely" or as a *routine* part of every physical examination? Because the bowel which is located within the bony pelvis is either difficult or impossible to visualize by radiography, endoscopy for a distance of *at least* 15 cm. from the anal verge is minimal. An insurmountable difficulty may be anticipated in about 15 per cent of patients who have an unyielding angulation of the bowel at about the level of 15 cm. from the anal verge. Since this level is the usual site of perforation, extreme caution should be exercised in this group of patients. Mild angulation of the bowel to the right or left side which exists in another 30 to 40 per cent of patients can be overcome by gentle manipulation. In the remaining 50 per cent of patients sigmoidoscopy offers little, if any, difficulty. The only real or major contraindication to endoscopy is an obstruction. Endoscopy should be discontinued promptly when the lumen of the bowel ahead of the scope is obscured by feces, blood, or an impassable lesion, or if the patient is unduly uncooperative or restless. This is particularly important in the unanesthetized juvenile patient as the sharp angulation of the sigmoid colon and the fragility of the bowel wall make laceration or perforation of the bowel wall easy.

For these and other reasons, the inexpert or the "occasional" endoscopist might do well to be satisfied with two-thirds of the loaf (15 cm.) until he has mastered or become very familiar with the technique of sigmoidoscopy using a 25 to 30 cm. sigmoidoscope. Several additional centimeters of the bowel beyond the reach of the sigmoidoscope can also be visualized with ease by the gentle use of air insufflation. This maneuver also flattens out redundant mucosal folds and may thus reveal small but hitherto hidden lesions. With experience pneumatic rupture of the bowel need not occur.

In spite of contrary views endoscopy may be attempted without preliminary preparation of the bowel by enemas; laxatives are practically never necessary. This policy is pursued in order to observe the unaltered mucosa and not to wash away important diagnostic clues such as blood, pus, and mucus which may harbor amebic trophozoites or other organisms coming from above the reach of the sigmoidoscope. Preparation is emphatically eschewed in known cases of colitis and similar clinical inflammatory states. As a result of this policy an increasing number of instances of unsuspected proctitis that supervened on constipation have been detected as well as malignancies in the colon that had not been detected by prior radiography. Also, by avoiding enemas, the inadvertent exacerbation of unsuspected inflammatory states in a number of patients can be avoided or prevented. Furthermore, the unprepared bowel makes endoscopy simpler and cleaner to execute and more susceptible to frequent examination, especially by the busy nonspecialist. Over 65 per cent of my patients are successfully sigmoidoscoped without preliminary enemas. The remaining 35 per cent of the patients either return at a later date for endoscopy after preparation or are given a concentrated packaged hypertonic phosphate salts enema in the office and are examined within 10 to 15 minutes. Significantly, a concentrated enema should not be administered to a patient with intestinal symptoms before the character of the mucosa has been observed at least by rectoscopy. The hypertonic phosphate enemas are not totally free from harmful local side effects; they may also give rise to considerable sodium retention. To circumvent these deficiencies a concentrated sugar (Sorbitol) enema with dioctyl potassium sulfosuccinate, a wetting agent or detergent, is infrequently employed.

Ideas have consequences. The alert clinician does not rest his laurels after the performance of endoscopy. The presence of symptomatology referable to the alimentary tract, particularly bleeding via the anus, whether occult or gross, altered or unaltered, in addition to endoscopy, calls for a stool examination for parasites and so forth, and the newer special techniques of radiography of the colon which are repeated whenever this examination is equivocal. Also, the finding of benign, nonneoplastic lesions, especially internal bleeding hemorrhoids, is never accepted as the cause of gastrointestinal bleeding without further investigation. By the same token, patients with unexplained iron deficiency anemia should never be denied a proctoscopic survey to determine the presence of internal bleeding hemorrhoids, adenomas, or even cancer. These lesions may be the source of the slow or chronic blood loss which, when accompanied by a

blood volume deficit, may mimic a clinical picture of organic heart disease. The reverse is also sometimes true: blood loss from the rectum with resulting anemia is explained by existing hemorrhoids, and a systemic disorder, such as a blood dyscrasia, is overlooked for some time.

All suspicious and grossly apparent accessible lesions should be biopsied and these specimens as well as exudates or suspicious mucus should be subjected to histopathologic, bacteriologic, or chemical examination. In the case of adenomas the specimen should be removed at the base in order to detect malignant invasion. This procedure, in contrast to fractional biopsy, is designated as "total biopsy." Whereas sigmoidoscopy should be carried out by all clinicians, biopsy should be performed by only those capable of caring for possible immediate complications.

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